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CME MOC

# Cleveland Clinic Journal of Medicine

'All that wheezes is not asthma'

Palatal mass with an overlying white lesion

Guidelines on pharmacotherapy for perinatal depression

Treating perinatal depression: A call to action

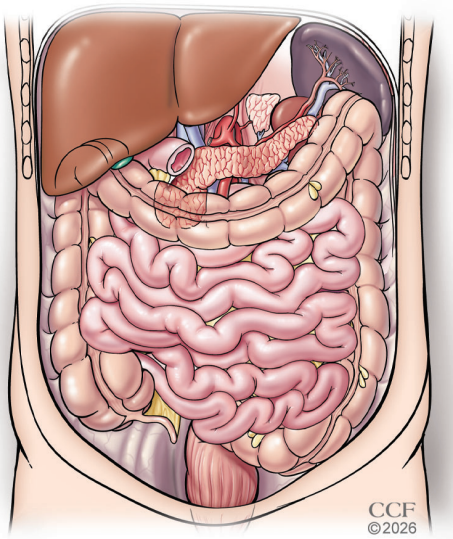
A 20-year-old woman with a 9-year history of dyspnea

DIGIT-HF: Time for a new look at digitalis?

Complement inhibition: A whole new world

A historical view of complement's clinical application

Gastrointestinal disorders in patients with diabetes mellitus



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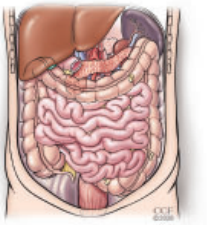

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# ‘All that wheezes is not asthma’—a reminder that the physical examination matters

An educational goal for our Symptoms to Diagnosis series, edited by Dr. Gregory Rutecki, is to give readers the opportunity to work through a patient’s clinical course along with the treating physicians, sharing some of their diagnostic and therapeutic cognitive branch points. At times, the series highlights missed opportunities in diagnosis and treatment that became evident over time. For those of you who enjoy the experience of working through these “cases,” I suggest that you stop and first read the paper in this issue by Johnson et al[1] about the treatment of a “20-year-old woman with a 9-year history of shortness of breath.”

The young woman in the article had a nearly decade-long history of significant dyspnea on exertion and had recently immigrated to the United States. There are many potential contributors to the delay in her diagnosis, particularly following her arrival in the United States, including language barriers and fears of accessing medical care due to her immigrant status. The impact of social determinants on her medical care likely played a role in the delayed diagnosis and should not be dismissed, but the major teaching points relate to the many opportunities where the physical examination and a reflective review of her medical history could have led to an earlier diagnosis. A marked delay in the diagnosis of upper airway obstruction, which is frequently treated as refractory asthma, is quite common.[2,3]

Stridor is an uncommon clinical finding that we should promptly recognize and distinguish from wheezing. Unlike the expiratory wheeze of asthma, which is best appreciated over the lungs, stridor is a high-pitched sound produced by turbulent airflow through a narrowed upper airway. It is heard best from the suprasternal notch upward to over the trachea. It may be loud enough to be heard without a stethoscope. Stridor, unlike the wheezing of bronchospasm, is characteristically more prominent during inspiration than expiration[2] and may be biphasic. This contrasts sharply with asthma, where expiratory wheezing predominates over the lung fields and only rarely radiates loudly to the trachea. Hearing a prominent inspiratory component is distinctly unusual and should prompt checking for an upper airway obstructive process.

Beyond auscultation, clinicians should assess for associated historical features and physical findings. The presence or history of a saddle-nose deformity, auricular chondritis, or nasal septal perforation suggests the need to consider the diagnosis of granulomatosis with polyangiitis or relapsing polychondritis. These uncommon conditions can also be suggested by a clinical history or unexplained laboratory findings consistent with a systemic inflammatory disease. A history of previous intubation raises the possibility of delayed traumatic airway stenosis.

Vocal cord dysfunction, also termed paradoxical vocal fold motion, deserves special emphasis, as it frequently masquerades as severe asthma and often is unrecognized for years.[3,4] This condition involves inappropriate adduction of the vocal cords during inspiration, creating airflow limitation

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at the laryngeal level accompanied by stridorous breathing. In a seminal study of 95 patients with vocal cord dysfunction,[5] 42 were misdiagnosed with asthma for years, with most patients having received high-dose glucocorticoids on multiple occasions. They received an incorrect diagnosis despite the fact that expiratory wheezing over the lung fields is a rare finding in patients with vocal cord dysfunction. These patients averaged 6 hospitalizations yearly, and 28% required intubation. Dyspnea was often worse during exercise, but significant oxygen desaturation was uncommon. Importantly, bronchodilator therapy was rarely effective. The diagnostic test for vocal cord dysfunction is direct visualization of vocal cord adduction during inspiration. Pulmonary function tests (PFTs) may reveal a flattened inspiratory flow loop—a component of PFTs that is often overlooked—and do not demonstrate reversible smaller airway obstruction.

Relapsing polychondritis is a rare autoimmune disorder characterized by recurrent inflammation of cartilaginous structures, including the trachea. Airway involvement occurs in 21% to 70% of patients with relapsing polychondritis and may be the initial manifestation, presenting as some combination of dyspnea, hoarseness, and tracheal tenderness.[6] Notably, for those with relapsing polychondritis or vocal cord dysfunction, marked anxiety can be a prominent (and understandable, once the diagnosis is confirmed) component of the patient's history and may lead to a delay in diagnosis.

Granulomatosis with polyangiitis may involve the large airways, and the subglottic area is a common site of airway involvement.[7] Subglottic stenosis may be the presenting component of the disease, particularly in young patients. Airway symptoms include voice changes, dyspnea, and cough, with the physical finding of stridor present on examination as the narrowing progresses. In patients with granulomatosis with polyangiitis, there may also be significant sinus and lung involvement, which may delay recognition of the upper airway involvement. As subglottic stenosis often does not respond to systemic therapy, it may not be recognized until other components of the disease respond to treatment while dyspnea persists.

Isolated subglottic stenosis can occur following traumatic intubations, but can also be idiopathic or congenital. If relatively mild, congenital stenosis may not be diagnosed until adolescence or adulthood[8]; sometimes there is a genetic predisposition,[9] as may have been the case in the patient described by Johnson et al.[1]

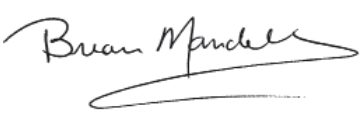
Evaluation of stridor in adults requires integration of the history, physical examination, and objective testing. The patient's history should assess the timing of symptoms related to exercise, their response to bronchodilators, and the presence of triggers (eg, environmental irritants, gastroesophageal reflux, postnasal drip) and include a thorough review of symptoms. Physical examination should be thorough and include auscultation of the chest and neck and assessment of the upper airway, sinonasal passages, skin, and ears.

As appropriate for most patients with undefined respiratory symptoms, PFTs should be obtained, and these should include a bronchodilator challenge. PFTs may relieve the suspicion for bronchospasm, although subglottic stenosis and distal airway obstruction may rarely coexist.[10] Direct visualization remains the gold standard for definitive diagnosis. Flexible nasolaryngoscopy or laryngoscopy can identify vocal cord dysfunction, subglottic stenosis, and supraglottic pathology. Bronchoscopy permits wider evaluation of the airways and may reveal mucosal inflammation, distal stenoses, or malacia not apparent on imaging.

But it is the physical examination, particularly the location and timing of abnormal breath sounds, that can provide the clues to the diagnosis and direct further testing. Inspiratory stridor heard over the trachea, especially with the associated lack of a physiologic response to bronchodilators, and a fairly normal oxygen saturation measurement during an episode of acute dyspnea suggest upper airway obstruction rather than asthma. Recognizing these findings on physical examination can prevent years of misdiagnosis and possible inappropriate treatment.

This topic was similarly discussed by Bhat and Ashton[11] in the *Journal* 5 years ago.

*Note: The adage "all that wheezes is not asthma" is attributed to Chevalier Jackson (1864–1958) by Strong and Vaughan.*[12]



Brian F. Mandell, MD, PhD
Editor in Chief

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April 29–May 1
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## MAY

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## JUNE

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June 6
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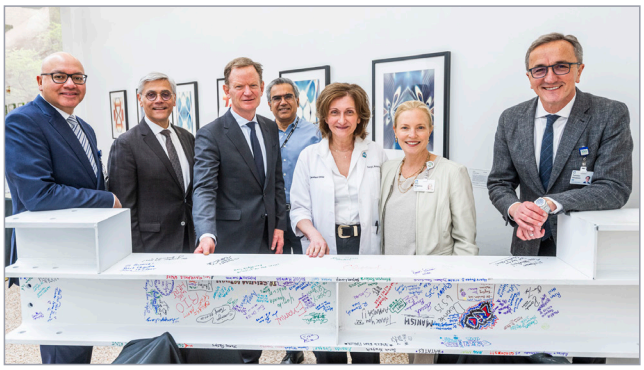

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# Finding the cause of severe hypokalemia

**To the Editor:** We read with great interest the article in the December issue by Dr. Leiva-Murillo and colleagues[1] in which the authors present a salient diagnostic approach for hypokalemia. One additional diagnostic consideration in the typical evaluation of severe hypokalemia is the presence of a covert eating disorder in the form of bulimia nervosa.

Regardless of the specific mode of purging used (self-induced vomiting, stimulant laxatives, or diuretics), these behaviors are frequently associated with the presence of hypokalemia, often with a concomitant metabolic alkalosis.[2] Because many patients with bulimia are often of normal body weight, these individuals can hide their history and can go undetected in the absence of anorexia nervosa and its characteristic thin habitus. Moreover, these patients tend to frequent busy emergency departments, urgent care centers, and student health centers, where clinicians have limited time to delve into the potential causes of the hypokalemia.

A helpful approach to follow is that the presence of hypokalemia in an otherwise healthy-appearing young person may be a sine qua non of a covert eating disorder. It is important to make this diagnosis, given the lethality of eating disorders and the potential for the subsequent development of hypokalemic nephropathy[3] and edema due to pseudo-Bartter syndrome as a direct result of purging behaviors.[4]

Finally, similar to the patient whose case was presented in the article, patients with hypokalemia due to bulimia are treated with potassium chloride. Occasionally, on recheck a few hours later, the serum potassium level remains low. It is important to understand that the efficacy of potassium repletion is abrogated unless the contraction alkalosis resulting from dehydration due to purging behaviors is also corrected. This is known as pseudo-Bartter syndrome and is caused by the excessive aldosterone levels found in chronic bulimia resulting from increased aldosterone secretion to prevent critical dehydration from purging.

Philip S. Mehler, MD
Eating Recovery Center
University of Colorado School of Medicine,
Denver, CO

Dennis Gibson, MD
Eating Recovery Center
University of Colorado School of Medicine,
Denver, CO

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**In Reply:** We appreciate the thoughtful comments from Drs. Mehler and Gibson, which complement the diagnostic approach to hypokalemia presented in our article. In reply, we reinforce the association between electrolyte disturbances and eating disorders, highlight the electrolyte pattern that should raise suspicion for purgative behaviors, emphasize the need to address contraction alkalosis rather than treating hypokalemia in isolation, and note the importance of associated abnormalities such as hypomagnesemia that can complicate the management of hypokalemia.

We hope these clarifications further strengthen the practical approach to hypokalemia outlined in our original article.

Enmanuel A. Leiva-Murillo, MD
Hospital Clínic, University of Barcelona,
Barcelona, Spain

Erwin Bechtold-Javier, MD
Hospital Clínic, University of Barcelona,
Barcelona, Spain

Pol Candela-Parrilla, MD
Hospital Clínic, University of Barcelona,
Barcelona, Spain

Ana Matas-García, MD, PhD
Hospital Clínic, University of Barcelona,
Barcelona, Spain

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**Takuma Watanabe, DDS, PhD**
Junior Associate Professor, Department of Oral and Maxillofacial Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

# Palatal mass with an overlying white lesion

A 55-year-old woman presented with a mass and a white lesion on her hard palate. She said that the mass had been present for 15 years. She did not have any symptoms related to the mass, except for experiencing occasional food entrapment in the neck of the mass. She had a history of type 2 diabetes mellitus and no history of smoking or alcohol consumption.

Examination revealed a painless, firm mass on the hard palate with a nonscrapable white lesion on the overlying mucosa of the mass (**Figure 1**). Computed tomography did not show any notable abnormalities.

Based on these findings, a clinical diagnosis of torus palatinus with leukoplakia was made. Because an excisional biopsy of the leukoplakia was considered necessary, en bloc removal of the lesion and the torus palatinus was recommended. The patient declined the procedure, so we monitored her closely for 7 years. The leukoplakia disappeared over time, but the mass remained unchanged throughout the follow-up period. The leukoplakia was likely a reversible frictional keratosis.

**Figure 1.** The patient had a painless, firm mass on the hard palate and a white lesion attached to the overlying mucosa of the mass.

## TORUS PALATINUS

Torus palatinus presents as a median, symmetrical bony protuberance along the midline ridge of the hard palate. It is typically asymptomatic, often goes unnoticed, and is usually discovered by the patient or incidentally during routine dental examination.[1]

Torus palatinus is present in up to 25% of the general population and is more common in women.[1,2] It has a higher prevalence in East Asian populations than in West African populations; individuals between 20 and 50 years of age are most commonly affected.[3] A study that included 448 women from different ethnic groups living in the United States found torus palatinus was present in 25.6% (11 of 43) of Hispanic participants, 22.5% (68 of 302) of Black participants, 16.7% (6 of 36) of Asian participants, 16.1% (10 of 62) of White participants, and 0% (0 of 5) of Native American participants.[4] A study conducted in Malaysia reported a torus palatinus prevalence of 32.9% in Malaysian women.[5]

About 30% of palatal tori are hereditary, while the remaining 70% are thought to result from environmental factors such as masticatory hyperfunction (excessive chewing) and parafunctional habits such as bruxism and jaw clenching.[1,3]

Torus palatinus should be differentiated from other intraoral lesions, including fibromas, mucoceles, osteomas, osteochondromas, osteoid osteomas, and, most important, malignant tumors such as squamous cell carcinoma and chondrosarcoma (**Table 1**).[1,2] The diagnosis of torus palatinus is primarily clinical, but radiographic and pathologic examinations may occasionally be helpful.[1]

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**TABLE 1**
**Differentiating torus palatinus and malignant lesions of the hard palate**

| Characteristics | Torus palatinus | Malignant lesions of the hard palate |
|---|---|---|
| **Surface** | Smooth | Irregular |
| **Palpation** | Bony, hard | Soft |
| **Morphology** | Symmetrical | Asymmetrical |
| **Growth** | Minimal, slow | Rapid |
| **Onset** | Gradual | Acute, sudden |

Treatment is generally not required for asymptomatic patients[3]; however, surgical removal may be considered when there are concerns related to trauma, hygiene, psychological distress, or functional impairment.[1] The mucosa covering palatal tori is often thin and prone to trauma, which may lead to ulceration or inflammation.[1] Additionally, white, nonscrapable lesions such as frictional keratosis, lichen planus, or leukoplakia can develop on the surface.[6] These lesions are commonly encountered by dental surgeons, dermatologists, and otolaryngologists; they require careful monitoring because of the potential for malignant transformation into, for example, squamous cell carcinoma.[2,6]

## DISCLOSURES

The author reports no relevant financial relationships which, in the context of their contribution, could be perceived as a potential conflict of interest.

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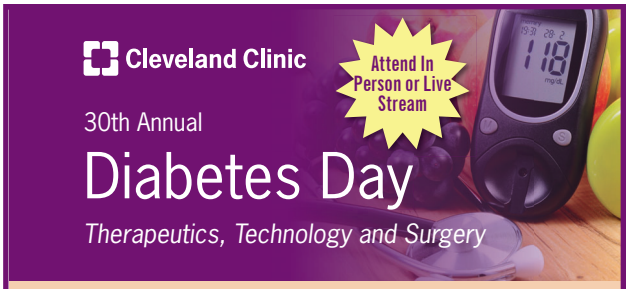
*Address: Takuma Watanabe, DDS, PhD, Department of Oral and Maxillofacial Surgery, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan; takuma@kuhp.kyoto-u.ac.jp*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**Zehra Aftab, MD**
Department of Psychiatry, University of Chicago, Chicago, IL

**Nicole Leong, MD, MS**
Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL

**Jason Alexander, MD**
Department of Medicine, Division of General Internal Medicine, University of Chicago, Chicago, IL

# Updated guidelines for pharmacologic treatment of perinatal depression: Understanding medication options

## ABSTRACT

The 2023 American College of Obstetricians and Gynecologists (ACOG) guideline on perinatal mental health conditions recommends prescribing and titrating pharmacotherapy for perinatal depression, with the selective serotonin reuptake inhibitors sertraline and escitalopram as first-line medications for patients who have not previously taken any medications for mood disorders. A subsequent ACOG Clinical Practice Update addresses zuranolone for postpartum depression. The authors present an overview of the guideline's recommendations on pharmacotherapy for treating perinatal depression and summarize actionable recommendations for nonpsychiatric clinicians.

## KEY POINTS

- Selective serotonin reuptake inhibitors are recommended as first-line pharmacotherapy for perinatal depression; serotonin norepinephrine reuptake inhibitors are reasonable alternatives.
- Continue or represcribe previously effective pharmacotherapy. If newly initiating pharmacotherapy, sertraline or escitalopram is recommended.
- When prescribing and titrating pharmacotherapy, use a validated screening tool to monitor treatment response with the goal of symptom remission.
- Zuranolone, a synthetic allopregnanolone analogue, can be considered for postpartum patients with depression who may benefit from rapid medication onset.

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Perinatal depression is defined as a major depressive disorder that occurs during pregnancy or within 4 weeks after delivery,[1] though most clinical experts suggest extending the time period to 12 months postpartum.[2] Due to abrupt declines in progesterone levels after delivery, perinatal depression can differ physiologically from depression not related to pregnancy. An estimated 10% of pregnant and 21.9% of postpartum patients experience depression,[3] yet only 20% receive adequate treatment.[4] Patients who discontinue antidepressants during pregnancy have a higher risk of depression than those who continue pharmacotherapy.[5] The Edinburgh Postnatal Depression Scale is effective at identifying patients with postpartum depression.[3]

*See related editorial, page 207*

This article summarizes recommendations pertaining to pharmacotherapy for perinatal depression from the 2023 American College of Obstetricians and Gynecologists (ACOG) clinical practice guideline.[2] Other psychiatric conditions that can develop during the perinatal period, including bipolar disorder, anxiety disorders, and postpartum psychosis, are discussed in the guideline but not reviewed here.

While the 2023 ACOG guideline recommended consideration of intravenous brexanolone, a synthetic progesterone metabolite and the first medication approved by the US Food and Drug Administration (FDA) specifically for postpartum depression, it was

removed from the commercial market in January 2025.[6] A similar oral agent, zuranolone, was approved by the FDA in August 2023 to treat depression in postpartum patients. ACOG recently published a Clinical Practice Update[7] on zuranolone because it was approved after the 2023 guideline was released. Evidence on zuranolone and its utility in clinical practice is also discussed here in the context of the guideline recommendations.

## WHO IS THE INTENDED AUDIENCE?

The updated 2023 guideline primarily addresses obstetricians and physicians caring for pregnant and postpartum patients, but the recommendations are relevant for any clinician caring for a patient in the preconception, pregnancy, or postpartum periods. As primary care clinicians play a key role in supporting mental health during the perinatal period, including prescribing medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) and facilitating referrals to psychotherapy, this guideline is applicable to many nonpsychiatric clinicians.

## WHO WROTE THE GUIDELINES?

The original 2007 ACOG guideline on the use of psychiatric medications during pregnancy and lactation was updated in 2008.[8] The 2023 guideline[2] provides updated evidence-based recommendations from a guideline committee that was composed of obstetricians, with consultation from 2 psychiatrists. The guideline includes recommendations for pregnant or postpartum individuals with depression; anxiety and anxiety-related disorders; bipolar disorder; and acute psychosis with onset predating pregnancy, onset or exacerbation during pregnancy, or 1 year post partum.

## WHAT ARE THE MAIN RECOMMENDATIONS?

**A validated screening tool** should be used to monitor treatment response and titrate medications to achieve the goal of symptom remission when using pharmacotherapy. In a sequential case series of 10,000 mothers, 1,396 had a positive screening result on the Edinburgh Postnatal Depression Scale (score ≥ 10), and 68.5% were subsequently diagnosed with unipolar depressive disorder.[3] Most (66%) had a comorbid condition, of which 82.9% were anxiety disorders.

**Pharmacotherapy, psychotherapy, or both** are recommended as first-line treatment for perinatal depression. Many perinatal depression treatment recommendations are extrapolated from those for the general population.[9,10]

**SSRIs** are recommended as first-line pharmacotherapy, and **SNRIs** are reasonable alternatives during pregnancy and post partum.

A randomized controlled trial of 254 women in England with postpartum depression (defined as Edinburgh Postnatal Depression Scale score ≥ 13) compared pharmacotherapy using 1 of 5 first-line SSRIs with "listening visits." Participants initially randomized to pharmacotherapy were more likely to have improved Edinburgh Postnatal Depression Scale scores (< 13) after 4 weeks vs those receiving listening visits (45% vs 20%, odds ratio 3.4, 95% confidence interval 1.8–6.5, $P < .001$).[11]

**Sertraline and escitalopram** are the recommended first-line medications for patients with no previous pharmacotherapy use. Sertraline is preferred because of its well-established safety profile and high remission rates. In a randomized controlled trial of 36 participants with postpartum depression, 59% of those receiving sertraline 50 to 200 mg for 6 weeks demonstrated clinical response (defined as Hamilton Depression Rating Scale score ≤ 10, 50% reduction in baseline score, and improvement in Clinical Global Impression score) compared with 26% of the placebo group ($P = .05$).[12] Increased remission rates (Hamilton Depression Rating Scale score ≤ 7) were seen in 53% of the sertraline group vs 21% of the placebo group ($P = .05$).

The guideline also recommends escitalopram as an alternative because it is safe, effective, and well tolerated.

**Reinitiation of a previously effective medication** should be considered as first-line treatment during pregnancy or post partum.

**Withholding or discontinuing antidepressant medications** during pregnancy or due to lactation status alone is not recommended, as discontinuation is associated with an increased risk of depression and destabilization.[5] Additional risks of discontinuation include preterm birth, impaired infant attachment, and suicide, and these risks must be balanced against the low risk of persistent pulmonary hypertension of the newborn and transient neonatal adaptation syndrome.[2]

Evidence suggests that the benefits of pharmacotherapy outweigh the risks. Studies have shown small, inconsistent associations between SSRIs and SNRIs and neonatal risks.[2] While some studies evaluate specific antidepressant medications separately, many combine several SSRIs and SNRIs and study their effects compared with no antidepressant use. This makes it

difficult to compare them directly. Exposure to SNRIs in the first trimester may carry a small increased risk of preeclampsia and spontaneous abortion. First-trimester paroxetine exposure may be associated with an increased risk of birth defects compared with other SSRIs.[8]

A cohort study of 949,504 women enrolled in Medicaid evaluated first-trimester antidepressant medication exposures and found no increased risk of infant cardiac malformations in those taking SSRIs (odds ratio 1.06, 95% confidence interval 0.93–1.22) or SNRIs (odds ratio 1.20, 95% confidence interval 0.91–1.57).[13]

There is also little evidence that suggests SSRIs or SNRIs increase the risk of postpartum hemorrhage.[2]

Overall, the benefits of treatment are clear, whereas the risks of first-line medications are small and inconsistently described.

**Zuranolone**, a daily oral synthetic allopregnanolone, should be considered for treating depression in postpartum patients with moderate to severe depression now that brexanolone, which was included in the 2023 guideline, is no longer commercially available.

Postpartum depression is influenced by many physiologic and environmental factors, including hormones.[14,15] Progesterone levels rapidly decline after childbirth. Reduction of allopregnanolone, a progesterone metabolite, is associated with postpartum depression via reduced modulation of gamma-aminobutyric acid A receptors.[16,17] Given this understanding of unique hormonal contributions to the pathophysiology of postpartum depression, novel neurosteroid treatments have been of great interest. FDA approval of the first oral medication for postpartum depression is an advancement in treatment.

Phase 3 randomized controlled trials have compared zuranolone with placebo for severe postpartum depression.[16,17] In 150 patients who were 6 months or less post partum and had depression onset between the third trimester and 4 weeks after delivery, zuranolone 30 mg for 14 days improved Hamilton Depression Rating Scale scores compared with placebo at day 15 (least squares mean difference −4.2, 95% confidence interval −6.9 to −1.5, $P = .003$).[16] Significant improvement was observed from days 3 through the end of the 45-day follow-up period.

A separate study evaluating zuranolone's efficacy on symptom improvement in patients with major depressive disorder outside of the perinatal period found improvement with a once-daily 50-mg dose.[18] This prompted evaluation of zuranolone 50 mg for postpartum depression.[17] In 196 patients with postpartum depression receiving zuranolone 50 mg for 14 days, Hamilton Depression Rating Scale scores similarly improved at day 15 compared with placebo (least squares mean difference −4.0, 95% confidence interval −6.3 to −1.7, $P = .001$), with improved remission rates from days 3 through 45.[17]

Treatment-emergent adverse events were reported by 60.2% of participants receiving zuranolone 50 mg compared with 41.8% for placebo; dizziness and somnolence were the most common.[17] Fifteen percent of patients in both the zuranolone 50-mg and placebo groups took concomitant antidepressants, which were mostly SSRIs (68.2% and 94.1%, respectively). Lower adverse event rates were reported in those taking lower doses (30 mg and 40 mg).[16,19]

## WHAT DIFFERS FROM PREVIOUS GUIDELINES?

The most impactful change from previous guidelines is the recommendation to use pharmacotherapy for perinatal mood disorders. The 2008 guideline[8] reviewed the safety data of SSRIs, SNRIs, benzodiazepines, tricyclic antidepressants, and mood stabilizers to treat perinatal mood disorders but did not recommend pharmacotherapy. The 2023 guideline[2] updated the recommendation to initiate and titrate medications for perinatal depression based on data from several trials.

## DO OTHER SOCIETIES AGREE OR DISAGREE?

The third edition (2010) of the practice guideline for the treatment of patients with major depressive disorder from the American Psychiatric Association[20] includes a section on pregnancy and postpartum. Similar to the 2023 ACOG guideline, the American Psychiatric Association recommends pharmacotherapy for treating depression with onset before pregnancy, favoring a particular antidepressant that has worked for the patient in the past and using a single agent whenever possible. For patients with new-onset perinatal depression, the American Psychiatric Association describes, but does not explicitly recommend, prescribing antidepressants according to the same principles for other types of major depressive disorders.

## HOW WILL THIS CHANGE DAILY PRACTICE?

Mental health conditions are a leading cause of perinatal mortality,[7] yet few clinical trials have been conducted on effective treatments during pregnancy. Identifying and treating perinatal depression decreases the risk of substance use, disengagement in care, low birth weight, preeclampsia, relationship disruption, self-harm, and suicide.[2]

**TABLE 1**
**First-line pharmacotherapy options for perinatal depression**

| Medication[a] | Starting dose | Initial increase after 4 days[b] | Increase after 4-week reassessment | Therapeutic range |
|---|---|---|---|---|
| Sertraline | 25 mg | By 25 mg to 50-mg dose[c] | By 50 mg | 50–200 mg |
| Fluoxetine | 10 mg | By 10 mg to 20-mg dose | By 20 mg | 20–80 mg |
| Citalopram | 10 mg | By 10 mg to 20-mg dose | By 10 mg | 20–40 mg |
| Escitalopram | 5 mg | By 5 mg to 10-mg dose | By 10 mg | 10–20 mg |

[a]Sertraline and escitalopram are preferred.
[b]Consider slower titration (after 10–14 days) in patients who are medication naive.
[c]If symptoms are inadequately controlled, may increase to total dose of 100 mg after maintaining a dose of 50 mg for at least 7 days.

Adapted from reference 2.

## Universal screening for perinatal depression

Clinicians should screen all perinatal patients for depression by using a validated instrument. The Edinburgh Postnatal Depression Scale and Patient Health Questionnaire-9 are easily administered and effective at identifying patients with perinatal depression.[2,3]

Patients who have a positive screening result, or those who report depression symptoms, should be assessed with a careful history of past diagnoses and treatment trials, including medications (dosages, effectiveness, side effects) and psychotherapy. Patients with perinatal depression symptoms who are already taking an SSRI or SNRI should continue treatment, and the dose should be titrated up. Those who were previously treated with an effective SSRI or SNRI should be restarted on the lowest dose and titrated up until symptom remission. For medication-naive patients, the guideline recommends starting first-line treatment with sertraline or escitalopram, reevaluating within 4 weeks, and titrating up to symptom remission (**Table 1**).[2]

Patients should be referred to a psychiatrist if they develop significant side effects or treatment resistance to an SSRI or SNRI, or have a history of or active bipolar disorder, postpartum psychosis (a psychiatric emergency), or postpartum obsessive-compulsive disorder.

## Selecting the right medication

**SSRIs and SNRIs** remain affordable, accessible, and safe for the duration of perinatal depression. Given the high prevalence and low treatment rates of perinatal depression, implementing these recommendations has the potential to benefit patients, neonates, and families, with minimal risk.

Strategies to optimize medication response and minimize side effects include the following:

- Select a single agent
- Start with the lowest dose and titrate up
- Monitor response with validated instruments such as the Edinburgh Postnatal Depression Scale
- Minimize medication transitions
- Avoid discontinuing effective medications due to pregnancy alone
- Provide psychotherapy and social support.

**Zuranolone** should be considered for postpartum patients who experience significant SSRI or SNRI side effects, those already on a high-dose SSRI or SNRI, or those who would benefit from rapid medication onset. Although few patients in zuranolone trials took concomitant SSRIs, limiting interpretation of its efficacy in SSRI-refractory postpartum depression, a 2024 indirect treatment comparison estimated that postpartum depression treatment with zuranolone resulted in larger decreases in Edinburgh Postnatal Depression Scale scores compared with SSRIs.[21]

The recommended starting dose is 50 mg, which can be titrated down to 40 mg if a patient experiences significant side effects such as dizziness or somnolence.[19] The dose should be reduced to 30 mg for patients with severe hepatic impairment (Child-Pugh class C liver cirrhosis), estimated glomerular filtration rate less than 60 mL/min/1.73 $m^2$, or concurrent use of a strong cytochrome P450 3A4 inhibitor.[19] Similar improvements were seen at 15 days in patients taking 30-mg and 50-mg doses,[16,17] though the doses were not directly compared with each other or against first-line SSRIs.

Of note, zuranolone may require insurance prior authorization and is only available from specialty pharmacies, necessitating prescriber familiarity or assistance from an experienced pharmacist.

Further studies are needed to better understand the safety and efficacy of pharmacotherapy, including SSRIs and SNRIs, for perinatal depression. Additional zuranolone studies are also warranted, especially comparing its effectiveness with SSRIs or SNRIs, effectiveness between doses, administration during pregnancy, safety and efficacy with adjunctive therapies, benefits beyond 45 days, and effects on lactation.

## WHEN WOULD THE GUIDELINES NOT APPLY?

The transient depressive condition immediately after childbirth that lasts 10 days or less, colloquially referred to as *postpartum blues*, does not meet the criteria for perinatal depression and does not require medication.[20] Patients who develop depression symptoms in the perinatal period and have a history of mania or other prior psychiatric diagnosis should be treated according to standard guidelines for either bipolar disorder or the preceding psychiatric diagnosis.

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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***Address:*** *Rebeca Ortiz Worthington, MD, MS, CLC, Department of Medicine, Division of General Internal Medicine, MC 3051, University of Chicago, 5758 South Maryland Avenue, Chicago, IL 60637; Rebeca.OrtizWorthington@bsd.uchicago.edu*

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EDITORIAL

**Lulu Zhao, MD**
Co-Director, Women's Behavioral Health, Cleveland Clinic, Cleveland, OH; Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Treating perinatal mood and anxiety disorders: A call to action

When Cohen et al[1] published their 2006 landmark study on relapse of depression during pregnancy, they stated in the Comment section, "There has been a common belief that characteristic hormonal changes associated with pregnancy are inherently 'protective' with respect to … depression … and that discontinuation of psychiatric medications should be almost uniformly pursued given concerns regarding prenatal exposure to these agents."

We now know that pregnancy confers no such protection. One in 5 individuals giving birth in the United States experiences a mood disorder during the perinatal period (during pregnancy or up to 1 year post partum).[2] Anxiety is the most common (20.7%),[3] followed by depression (12.1%).[4] Other conditions such as mania, postpartum psychosis, or posttraumatic stress disorder are less common, but can create an outsized effect on the health and life trajectories of those affected.

Various factors drive the high incidence of perinatal mood and anxiety disorders. During pregnancy, a massive influx of estrogen and progesterone, which are both sex hormones and neuroactive steroids, promote neuroplasticity.[2] Accordingly, the brain undergoes significant neuroanatomic remodeling during the perinatal period. These changes are most pronounced in the regions involved in emotional regulation and social cognition: the prefrontal cortex, hippocampus, and amygdala. The perinatal period thus invites parents to imagine new ways of relating to the world around them, and for individuals with biologic and psychosocial vulnerabilities, these new thought patterns may be maladaptive.

## MOOD DISORDERS ARE COMMON BUT OFTEN UNTREATED

Untreated perinatal mood and anxiety disorders create an environment of psychosocial toxicity that devolves into longitudinal adversity. Studies show that depressed parents are less able to engage in productive relationships, including with their newborn children.[2] Maternal depression in the postpartum year is also strongly associated with an increased unemployment risk for up to 15 years after childbirth,[5] with an estimated societal cost of nearly $31,800 per affected mother-child dyad over the first 6 years.[6] This can disproportionately impact the 41% of mothers who are primary earners.[7] Meanwhile, the leading cause of death for mothers in the first year post partum is untreated mental health disorders, outranking serious conditions such as hemorrhage and hypertensive disease.[8]

*See related article, page 201*

In 2015, the American College of Obstetricians and Gynecologists[9] began recommending universal depression screening in pregnancy, and the US Preventive Task Force[10] followed suit in 2016. A study of privately insured individuals showed that the perinatal mood and anxiety disorder detection rate rose 93% across all states, ages, races, and ethnicities from 2015 to 2020.[11] However, exactly what to do after a positive screening result still remains uncertain for many patients and clinicians.

Currently, perinatal mood and anxiety disorders remain untreated in 3 of 4 affected individuals giving birth,[12] and the discrepancy between needing care and receiving care is highest in our most vulnerable populations: the marginalized, the socioeconomically disadvantaged, the isolated, and the inadequately insured. More than half of US counties lack a practicing psychiatrist, and that statistic rises to 80% in rural counties.[13] While accessing a psychiatrist via telehealth might mitigate some of these shortages, the reality is that over a quarter of rural counties lack access to reliable broadband,[14] and some health insurance companies are choosing to restrict telehealth access now

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that the flexibilities enacted during the COVID-19 pandemic have expired.[15] Moreover, there are fewer than 500 specially trained reproductive psychiatrists in the entire United States, while more than 800,000 women each year experience perinatal mental health complications.[12]

## PRIORITIZING PERINATAL MENTAL HEALTH TREATMENT

Where does that leave our patients who struggle with their mental health while juggling the responsibilities of a growing family? Many will rely on the knowledge and judgment of non–mental health specialists, ie, obstetricians and primary care clinicians. It is noteworthy that more than half of women discontinue antidepressant medications during pregnancy.[16] Yet, 53% of these women will end up back on antidepressants in the postpartum period, as the risk of symptom recurrence is 50% to 70% even in those who were euthymic at the time of discontinuation.

### A risk-risk discussion

Treatment decisions during pregnancy should therefore be framed as a risk-risk discussion. Lack of treatment is not neutral—untreated perinatal mood and anxiety disorders themselves are associated with adverse obstetrical and neurodevelopmental outcomes.[2] Decades of quality, peer-reviewed research have demonstrated the favorable safety profile of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of medications for depression and anxiety.[17] Women with depression who are treated with SSRIs during pregnancy exhibit no clinically significant increased risk of miscarriage, fetal growth restriction, preterm birth, cesarean birth, or adverse neurodevelopmental outcomes compared with those with untreated depression.[18] SSRIs are also widely considered compatible with breastfeeding because low amounts of these medications pass into breast milk.[2]

Meanwhile, risks that do exist should be put into proper context. The baseline risk of birth defects in all pregnancies is about 3%.[19] Exposure to an SSRI during pregnancy, including paroxetine, increases the risk of birth defect by less than 1%.[17] Persistent pulmonary hypertension of the newborn occurs in an additional 1 to 2 per 1,000 infants when exposed to SSRIs during pregnancy,[20] but this serious illness can also occur in the absence of SSRI use.[2] In addition, poor neonatal adaptation syndrome can occur in 15% to 30% of infants exposed to an SSRI during pregnancy, but the symptoms are mild for most and resolve within 2 weeks after delivery.[20]

### Traditional antidepressants vs novel ones

Timing is another consideration that significantly impacts a patient's quality of life. Traditional antidepressants like SSRIs must be used for 4 to 6 weeks at a therapeutic dose to yield significant clinical benefit. Today, postpartum patients have access to a new medication class that mimics the action of progesterone metabolites at the gamma-aminobutyric acid receptor. The rapid onset of these medications can produce reductions in depression scores within days. While more research is needed on which populations benefit most from traditional antidepressants vs novel ones, patients and clinicians alike now have more options to treat these serious mental health conditions.

As Ortiz Worthington et al[21] discuss in this month's issue of the *Journal*, it is imperative that obstetricians and primary care clinicians achieve basic competency in managing psychiatric disorders during the perinatal period. If we hope to see improved mental wellness for our mothers, families, and communities, we must all play an active role.

## DISCLOSURES

Dr. Zhao reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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***Address:*** *Lulu Zhao, MD, Department of Obstetrics and Gynecology, WH20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; zhaol5@ccf.org*


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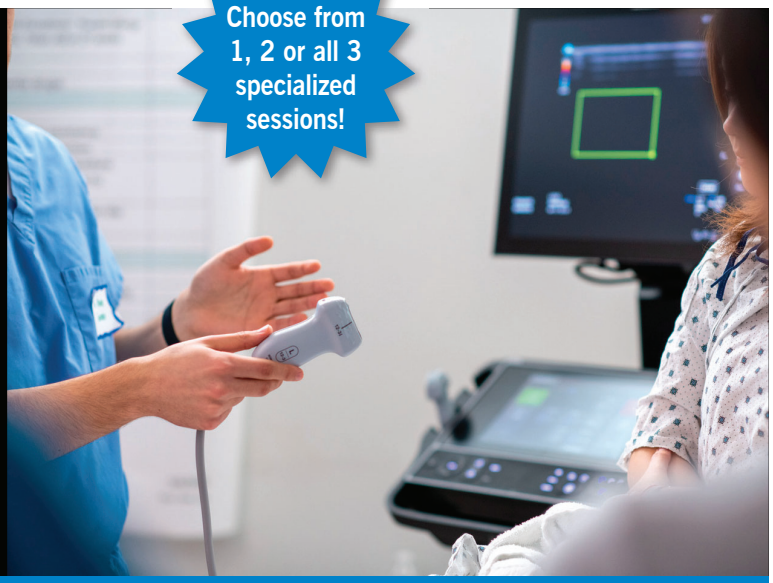


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**Mary C. Labanowski, MD**
Acting Medical Director, The Caridad Center, Boynton Beach, FL; Retired Associate Professor, Florida Atlantic University, Schmidt College of Medicine, Boca Raton, FL

# A 20-year-old woman with a 9-year history of shortness of breath

A 20-YEAR-OLD WOMAN presented to an internal medicine physician at our community-based free clinic due to increasing difficulty breathing. Her symptoms began 9 years earlier with the feeling of "something stuck in her throat." At that time she was living in South America and did not seek medical attention. Over the years, her shortness of breath progressively worsened without relief.

After immigrating to the United States at age 18, she was seen by a variety of clinicians and was given diagnoses of bronchitis, asthma, and COVID-19. She was treated with antibiotics, including tetracycline, erythromycin, and amoxicillin, as well as inhaled bronchodilators and steroids, without improvement.

Before presenting to our clinic, she was seen by a nurse practitioner, who documented decreased breath sounds and wheezing on physical examination and prescribed amoxicillin and guaifenesin. The patient knew that these medications did not improve her symptoms in the past and did not fill these prescriptions. She presented to our community-based clinic the following day and was not taking any medications.

On presentation, the patient complained of chest tightness and shortness of breath that worsened on exertion. She was having considerable difficulty performing normal activities of daily living, was unable to walk up a flight of stairs, had frequent nighttime waking due to shortness of breath, and had an intermittent nonproductive cough. She reported no fever, chills, night sweats, weight loss, or hemoptysis and did not have a history of tuberculosis or prior hospitalizations, surgeries, or intubations.

Her family history was significant for an older brother who experienced similar symptoms that resolved after surgery. She did not use tobacco, alcohol, or recreational drugs, and had no known history of occupational or toxic environmental exposures.

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## INITIAL EVALUATION

In the clinic, her temperature was 98.1°F (36.7°C), heart rate 96 beats per minute, blood pressure 105/60 mm Hg, respiratory rate 16 breaths per minute, oxygen saturation 97% on room air, and body mass index 25.7 kg/m$^2$.

On physical examination, she was neatly groomed but withdrawn. High-pitched inspiratory and expiratory sounds were audible without a stethoscope, and breathing was labored, engaging accessory muscles. The nares were patent. The oral cavity and oropharynx showed no erythema, exudate, masses, or lesions. The tonsils were not enlarged. Her voice was clear without hoarseness. There was no cervical adenopathy. Cervical musculature was bulky and prominent. Her trachea was midline, and thyroid was nontender without nodules and was not enlarged. Inspiratory and expiratory high-pitched sounds were most prominent with auscultation over the neck. Chest expansion was symmetrical. Lungs were clear to percussion and auscultation without wheezing or crackles.

Palpation of the chest revealed no abnormal pulsations, lifts, thrills, or heaves. Heart rate and rhythm were regular, with no extra heart sounds or murmurs. Abdomen was soft, without hepatomegaly, masses, or tenderness. There was no peripheral edema or nail clubbing.

## DIAGNOSTIC CLUES IN INITIAL FINDINGS

**1** Which aspects of this patient's presentation made the diagnosis of asthma less likely?

- ☐ Presence of biphasic stridor
- ☐ Shortness of breath and wheezing
- ☐ Duration of symptoms
- ☐ Lack of response to medications

A critical diagnostic clue in this patient's evaluation was the identification of stridor, distinct from

**TABLE 1**
**Categorization of stridor**

| Type[2] | Condition this type suggests | Common causes | Causes based on duration[4,5] |
|---|---|---|---|
| Inspiratory | Laryngeal obstruction (extrathoracic)[1] | Laryngeal edema<br>Laryngomalacia<br>Epiglottis (acute)<br>Vocal cord paralysis<br>Retropharyngeal abscess | Acute: epiglottitis, postextubation edema<br><br>Chronic: laryngeal tumor, trauma, vocal cord paralysis |
| Expiratory | Tracheobronchial obstruction (intrathoracic)[1] | Lower tracheal obstruction<br>Bronchial obstruction<br>Tumors<br>Tracheomalacia | Acute: tracheitis, foreign body aspiration to bronchus<br><br>Chronic: tracheal tumors, tracheomalacia |
| Biphasic | Glottic or upper trachea abnormalities[3] | Subglottic stenosis<br>Tracheal mass<br>Glottic abnormalities<br>Hemangioma<br>Foreign body | Acute: foreign body at glottis or upper trachea, postextubation edema<br><br>Chronic: subglottic stenosis, hemangioma, glottic scarring, granulomatosis with polyangiitis, retrosternal goiter, cricoarytenoid ankylosis |

wheezing. It is imperative to distinguish stridor from wheezing. *Stridor* is a physical finding described as a high-pitched respiratory sound produced by turbulent airflow through a partially obstructed airway.[1] It is loudest with auscultation over the neck, although at times it can be transmitted to the chest. *Wheezing* is also a high-pitched sound but originates from narrowing of the small airways of the lungs. Wheezes are loudest with auscultation over the lung fields, and minimally audible or absent over the neck.

Stridor is a much less common finding than wheezing but has multiple potential and serious etiologies (**Table 1**).[1–5] The categorization of this patient's stridor as chronic and biphasic narrows the diagnostic possibilities. The presence of stridor, particularly biphasic stridor, makes the more common diagnoses of asthma or bronchitis unlikely. Although severe asthma may present with biphasic wheezing, the sound is high pitched and loudest over the lung fields (rather than over the neck, as observed in our patient).

Asthma is a condition whose duration can be similar to the duration of symptoms seen in this patient, beginning in childhood and continuing into adulthood. An infectious process could exacerbate an underlying chronic respiratory issue like asthma[6]; however, upper respiratory infections are typically acute in nature,[7] while our patient's symptoms continued to progress over many years. Further, recurrent treatment of an acute problem without addressing the underlying chronic issue is ineffective. The patient was repeatedly treated with antibiotics, beta-agonist inhalers, and corticosteroids. Her lack of response to these treatments certainly put the diagnoses of bronchitis or asthma in question.

## INITIAL EVALUATION OF STRIDOR

**2** When stridor is suspected, which noninvasive diagnostic test is most useful in the initial evaluation?

- ☐ Pulmonary function tests (PFTs) with flow-volume loops
- ☐ Chest radiography
- ☐ Chest computed tomography
- ☐ Diffusing capacity of the lungs for carbon monoxide

### Pulmonary function testing

Treating hypertension without obtaining a patient's blood pressure or prescribing glasses without checking vision ignores the metrics that define the condition. In the same light, treating asthma without obtaining spirometry or full PFTs can result in both over- and underdiagnosis of asthma or a missed opportunity to diagnose other causes of respiratory symptoms.[8]

The diagnosis of asthma requires not only the presence of clinical symptoms of wheezing, shortness of breath, chest tightness, and cough, which fluctuate over time, but also documentation of variable expiratory airflow obstruction. A study of patients labeled as having persistent asthma, all of whom were treated in a single health system between 2016 and

**TABLE 2**
**The patient's spirometry results**

| | Predicted normal value | Before bronchodilator | % of predicted normal value | After bronchodilator | % of predicted normal value | % Change |
|---|---|---|---|---|---|---|
| FVC, L | 3.08 | 2.36 | 76 | 2.41 | 78 | 2 |
| $FEV_1$, L | 2.73 | 0.81 | 30 | 0.73 | 27 | –11 |
| $FEV_1$/FVC, % | 88 | 35 | | 30 | | |
| PEF, L/sec | 5.73 | 0.87 | 15 | 0.79 | 14 | –9 |

$FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow

2020, revealed that less than 15% had spirometry or PFTs ordered.[9] Another study reported that 30% to 35% of adults diagnosed with asthma did not have current asthma.[10] Furthermore, a recent case-finding trial showed that structured spirometry screening effectively identified previously undiagnosed asthma and chronic obstructive pulmonary disease.[11] The lack of early spirometry measurements and PFTs are often key contributors to delayed diagnoses in patients with respiratory symptoms.

**Updated technical standards for interpreting PFTs.** Clinicians should understand the biological variability and limitations of lung function testing.[12] When interpreting PFTs, clinicians must not only recognize patterns but also evaluate them in the clinical context to refine the differential diagnosis. In 2021, the European Respiratory Society/American Thoracic Society (ERS/ATS) joint task force updated its statement on PFT interpretation,[12] emphasizing that PFTs should be used to *classify physiology*, not to make a diagnosis. The ERS/ATS task force also updated its recommendation for testing severity of lung function impairment, suggesting that clinicians use the *z* score, which quantifies how many standard deviations a given lung function value is from the mean of a healthy population, instead of percent predicted because the *z* score provides more consistent data across age and sex categories.[12–14]

**The expiratory disproportion index** ([forced expiratory volume in 1 second ÷ peak expiratory flow] × 100) can effectively distinguish upper airway stenosis from other respiratory pathology, including vocal cord dysfunction and asthma (sensitivity 95.9%, specificity 94.2%), when a threshold value of 50 is used.[15–17] An expiratory disproportion index may be a valuable metric for assessing suspected airway obstruction and is widely accessible since it is derived from PFT results. However, it is not yet routinely included in the calculations in routine PFTs, and its accuracy may be limited in patients with obesity.

### Imaging options

A chest radiograph may be indicated in certain cases of stridor, particularly expiratory stridor, to help exclude extrinsic causes of airway obstruction such as mediastinal masses, lymphadenopathy, or foreign bodies. However, chest radiography and chest computed tomography often appear normal when biphasic stridor is present because these modalities have limited sensitivity for detecting lesions within the larynx or trachea.

In contrast, computed tomography of the neck can more precisely characterize structural abnormalities in the extrathoracic airway, such as subglottic stenosis, laryngeal masses, or external compression from thyroid enlargement or cervical lymphadenopathy, and is useful once categorization of stridor (**Table 1**) points to the neck as the source of the finding.

### Diffusing capacity of the lungs for carbon monoxide

This test measures gas exchange at the alveolar-capillary membrane. It is generally normal in isolated upper airway obstruction and offers little diagnostic value in this context.

## CASE CONTINUED: PULMONARY FUNCTION TESTING

Chest radiography revealed no acute disease, and the patient was referred to a pulmonologist for further evaluation with PFTs. Complete blood cell count and comprehensive metabolic panel were obtained and were normal.

This patient's PFT findings revealed good effort, with peripheral oxygen saturation of 99% on ambient air. Forced vital capacity was mildly reduced at 76% of predicted value (**Table 2**). Forced expiratory volume in 1 second and the forced expiratory volume in 1 second to forced vital capacity ratio were markedly reduced, at 30% of predicted and 35%, respectively, consistent with severe obstructive impairment. There was no improvement after a bronchodilator was administered.

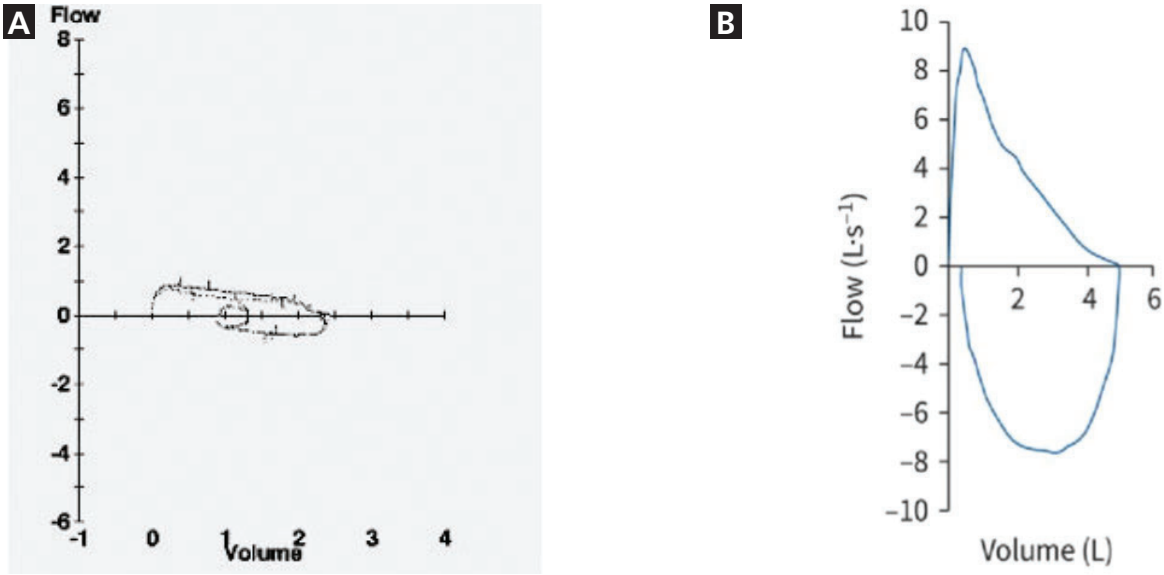


**Figure 1.** (A) The patient's spirometry flow-volume loop diagram showed truncation of both inspiratory and expiratory phases. (B) Typical flow-volume loop configuration.

Part B of this figure is adapted from Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J 2022; 60(1):2101499. doi:10.1183/13993003.01499-2021

The patient's $z$ score was −4.16,[18] indicating the highest severity level of lung function impairment per the ERS/ATS 4-tier $z$-score system.[12]

The patient's expiratory disproportion index was calculated as 93 ([0.81 ÷ 0.87] × 100), well above the threshold value of 50 for distinguishing upper airway stenosis from other respiratory pathology.

Flow-volume loop diagrams showed significant truncation of both the inspiratory and expiratory limbs, suggesting a fixed airway obstruction of the glottis or upper trachea (**Figure 1A**). This finding can differentiate fixed airway obstruction from vocal cord dysfunction, which presents with either a normal flow loop (**Figure 1B**) or a flattened inspiratory limb.

## DIFFERENTIAL DIAGNOSIS

**3** Which of the following diagnoses best explains this patient's clinical presentation and diagnostic findings?

- ☐ Asthma
- ☐ Cystic fibrosis
- ☐ Vocal cord dysfunction
- ☐ Subglottic stenosis

**Asthma** can have progressive symptoms and last many years, but the presence of stridor, rather than wheezing, as well as a lack of response to bronchodilators clinically and on spirometry, makes this diagnosis unlikely. Additionally, the patient was treated with agents for bronchospasm in the past without relief.

**Cystic fibrosis** is an inherited disease, with onset at a young age and ongoing progression. Cystic fibrosis is often characterized by chronic productive sputum, recurrent pneumonia, and gastrointestinal symptoms, none of which were part of her presentation. Findings of bronchiectasis on chest radiograph would also be expected with cystic fibrosis of this duration.

**Vocal cord dysfunction** presents with similar symptoms of shortness of breath, chest tightness, and stridor but does not have the PFT abnormalities seen in this patient. Also, the symptoms of vocal cord dysfunction are episodic, with intermittent periods of normal respiration, while the patient's symptoms were unremitting.

**Subglottic stenosis.** Her history of chronic progressive symptoms, findings of biphasic stridor on physical examination, normal chest radiograph, and abnormal spirometry with plateauing of both limbs of the flow-volume loop are consistent with the diagnosis of subglottic stenosis. Biphasic stridor is the classic primary presenting symptom of subglottic stenosis, both acquired and idiopathic.[4]

Subglottic stenosis is a rare entity, and the phenomenon of patients with subglottic stenosis being

misdiagnosed due to its similarities with other respiratory conditions is well documented.[5,15,19,20] One study suggests that 33% to 37% of all patients with subglottic stenosis are initially diagnosed with asthma and have a mean diagnostic delay of 2 years.[15]

In the outpatient setting, PFT findings can strongly suggest the diagnosis of subglottic stenosis. It is important to remember that a simple spirogram will not make this diagnosis. It is essential to order PFTs with flow-volume loop when evaluating stridor. The gold standard for diagnosing subglottic stenosis is laryngoscopy or bronchoscopy.[15]

## CASE CONTINUED: PULMONARY EVALUATION AND SURGICAL INTERVENTION

The pulmonologist suspected subglottic stenosis and ordered chest and neck computed tomography, which showed narrowing of the trachea (**Figure 2**), and subsequently referred the patient to an ear, nose, and throat (ENT) surgeon.

When the patient visited the ENT surgeon, her symptoms had worsened, and she was sent to a nearby emergency room, where she was admitted for airway observation. Initial inpatient bedside laryngoscopy showed evidence of 50% subglottic stenosis circumferentially. Later, while she was eating, she became acutely short of breath, and despite treatment with ipratropium bromide and albuterol sulfate inhalation solution, intravenous dexamethasone, and racemic epinephrine, she did not improve. She was sent to the operating room for emergent balloon dilation.

The patient underwent bronchoscopy and suspension microlaryngoscopy. (In this procedure, a rigid laryngoscope is inserted through the mouth to provide a direct microscopic view of the throat and vocal cords; the device is maintained in place by a "suspension" system, often placed on the patient's chest, to allow the surgeon use of both hands.) Laryngoscopy revealed the presence of 65% to 70% stenosis in a circumferential pattern that began at the cricoid level and extended about 1.7 cm (**Figure 3**). Balloon dilation together with blue laser–assisted removal of the stenosis substantially improved airway patency. Triamcinolone was injected throughout the subglottis. The patient was discharged home on acetaminophen and prednisone, with an outpatient ENT follow-up scheduled for 6 weeks after discharge.

Pathology reported respiratory mucosa with chronic inflammation and fibrosis, negative for granulomas.

The patient was seen by ENT in follow-up at the free clinic at 2 months. At that visit, fiber-optic laryngoscopy showed no stenosis. She was breathing comfortably without stridor, and she denied shortness of breath or dysphagia. Because all her symptoms had resolved, she canceled her primary care follow-up. The patient has moved out of the area and has not been seen at the community-based free clinic since.

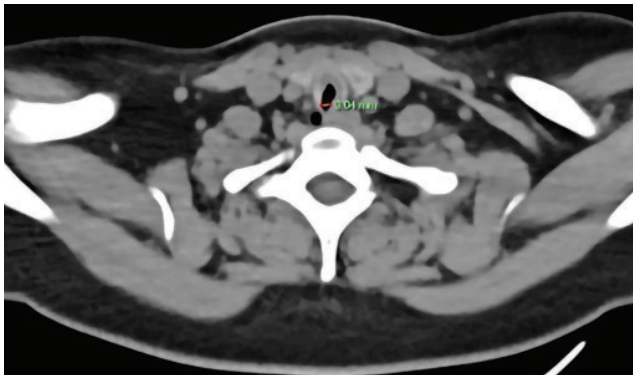

**Figure 2.** Neck computed tomography showed a narrowed trachea measuring 3.04 mm.

The patient's family history of a brother with similar symptoms that resolved after surgery raised the possibility of a genetic factor. Idiopathic subglottic stenosis is a rare condition with limited data, but there are reports of familial clustering in 2.5% of patients.[21] Congenital subglottic stenosis in siblings at birth and familial clustering in young women have also been reported. Neither pattern fit this patient's history.

## FACTORS THAT CAN LEAD TO DELAYED DIAGNOSIS

**4** Which of the following factors contributed to the delay in diagnosing subglottic stenosis in this patient?

- ☐ Breakdown in the patient-practitioner clinical encounter
- ☐ Lack of continuity of care
- ☐ Availability bias
- ☐ Limited economic resources

While it is difficult to evaluate the quality of a diagnosis, data suggest that 1 in 20 patients experience an error in outpatient diagnosis, and about half of those errors had the potential for patient harm.[22] This patient had symptoms for more than 9 years before the correct diagnosis was made and treatment provided. All of the listed factors contributed to this delay in diagnosis.

**Breakdowns in the patient-practitioner clinical encounter**, which includes the skills of history taking, physical examination, and ordering of diagnostic tests,

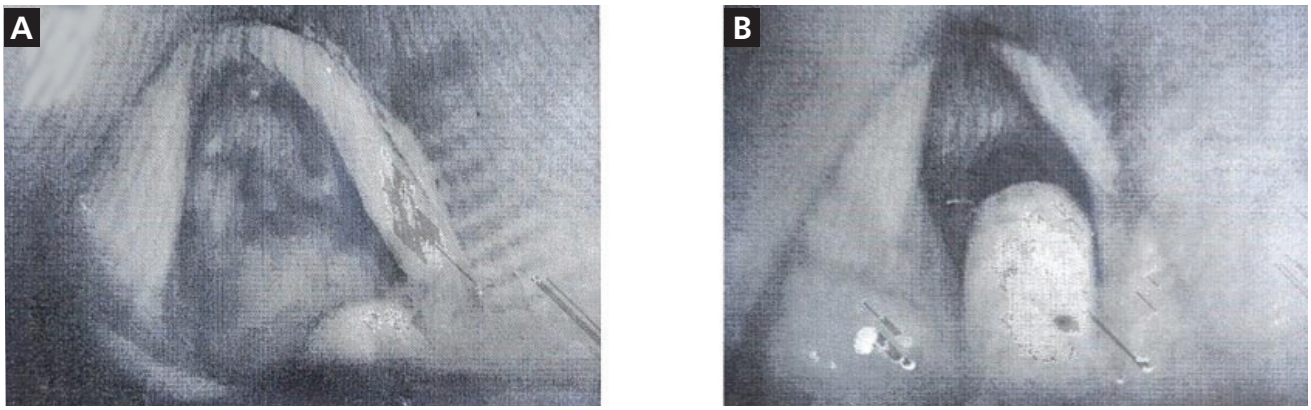


**Figure 3.** (A) Preoperative laryngoscopy revealed grade 2 subglottic stenosis (about 66% obstruction of the luminal area), with an airway caliber of about 5 mm. (B) Laryngoscopy after completion of the procedure showed no stenosis.

account for most errors in the outpatient setting.[23] All these factors played a part in the delay of this patient's diagnosis, specifically failure to identify the long history of progressive symptoms, acknowledge previous ineffective treatment, recognize the physical finding of stridor and its clinical significance, and order complete PFTs.

**Continuity of care** is a necessary component of optimal care but is often overlooked. Improved continuity of care lowers mortality rates, decreases hospital admissions, and reduces healthcare costs.[24,25] Unfortunately, continuity is frequently lacking, especially with the emergence of acute care and urgent care facilities, or as in this case, when the patient is transient and receives care through multiple free or low-cost clinics. A patient may see multiple clinicians without a central record or an ongoing therapeutic relationship. For our patient, lack of continuity meant that no single clinician had the chance to reevaluate the working diagnosis when her presumed wheezing failed to respond to the given treatment.

**Biases and social factors.** Multiple biases, both cognitive and implicit, have been identified that can derail the diagnostic process. *Availability bias* is the tendency to overestimate the likelihood of a certain event occurring when it readily comes to mind.[26] Clinicians influenced by a recent experience with a specific type of disease such as asthma or bronchitis may be more prone to misdiagnose diseases with similar signs and symptoms.[27] Problems may arise when the first impression is wrong, as clinicians are vulnerable to *anchoring bias* when they look for evidence to confirm their initial diagnosis and *premature closure* when they fail to consider alternative diagnoses.

A 2016 study with a dataset of more than 200 million patient records revealed that in the United States women consistently experience longer time to diagnosis than men.[28] The cause of this significant and consistent difference has not been elucidated, but the possibility that there is a systemic bias of discounting symptoms reported by women requires consideration and further investigation.

Studies have suggested that only 20% of an individual's health is due to the medical care they receive and that up to 50% is determined by social determinants of health.[29] The social determinants of health that affected this patient included limited economic resources, low health literacy, unstable safe housing, barriers to access to care, marginal financial resources, and limited transportation. Fortunately, free clinics exist to serve as the primary source of healthcare for uninsured patients; however, bureaucratic hurdles, discriminatory practices, stigma, and lack of social or financial capital remain.[30,31]

This patient's case highlights how insufficient diagnostic assessment, premature closure and other biases, interrupted continuity, and social determinants can combine to obscure an uncommon but critical diagnosis—reminding clinicians always to broaden the differential when symptoms do not improve and to remember that "all that wheezes is not asthma."

## TAKE-HOME POINTS

- It is critical to differentiate stridor from wheezing.
- In many patients who have central airway stenosis but no risk factors, the presence of stridor is often overlooked, leading to erroneous diagnoses of other respiratory diseases.
- Suspected airway obstruction should prompt early

evaluation with PFTs. Spirometry with flow-volume loops and calculation of the expiratory disproportion index are useful to identify and characterize stridor and upper airway obstruction.
- Normal chest radiography or chest computed tomography does not rule out pathologic airway obstruction.
- Engage a broad differential diagnosis when the expected response to treatment does not occur.
- Be aware of biases, diagnostic pitfalls, and social determinants of health that increase risk of missed or delayed diagnosis and treatment.

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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***Address:*** *Mary C. Labanowski, MD, Retired Associate Professor, Florida Atlantic University, Schmidt College of Medicine, 777 Glades Road, Boca Raton, FL 33431; mlabanowski@health.fau.edu*

**Enmanuel A. Leiva-Murillo, MD**
Department of Internal Medicine, Clinical Institute of Medicine and Dermatology, Hospital Clínic, University of Barcelona, Barcelona, Spain

**Oriol Ventosa-Blázquez, MD**
Department of Cardiology, Clinical Institute of Cardiovascular Diseases, Hospital Clínic, University of Barcelona, Barcelona, Spain

**Eduard Solé-González, MD, PhD**
Heart Failure and Heart Transplant Unit, Department of Cardiology, Clinical Institute of Cardiovascular Diseases, Hospital Clínic, University of Barcelona, Barcelona, Spain

# Interpreting the DIGIT-HF trial: Time for a new look at digitalis?

## ABSTRACT

The DIGIT-HF (Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure; N Engl J Med 2025; 393(12):1155–1165) trial compared digitoxin with placebo, added to guideline-directed medical therapy in patients with heart failure with reduced ejection fraction (HFrEF). Compared with placebo, digitoxin reduced the incidence of the composite endpoint of death from any cause or first hospitalization for worsening heart failure by 18% over a median follow-up of 36 months (hazard ratio 0.82, 95% confidence interval 0.69–0.98). There were no statistically significant differences in the rates of all-cause mortality, first hospitalization, or serious adverse events.

## KEY POINTS

- Digitoxin differs from digoxin in its pharmacokinetic properties.
- The trial used a pragmatic digitoxin dosing protocol, with a single serum level check at 6 weeks.
- The incidence of serious adverse events was numerically greater in the digitoxin group than in the placebo group (4.7% vs 2.8%), but the difference was not statistically significant.
- Digitoxin met the prespecified noninferiority criterion for all-cause mortality vs placebo, with a hazard ratio of 0.86 ($P < .001$); the threshold for noninferiority was 1.303.
- Digitoxin may confer a modest but clinically relevant benefit in patients with advanced, symptomatic HFrEF receiving optimal guideline-directed medical therapy.

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It may be time for a new look at some old drugs: in a large, randomized, placebo-controlled trial published in 2025, the cardiac glycoside digitoxin reduced the incidence of the combined endpoint of death from any cause or first hospitalization for heart failure when added to guideline-directed medical therapy in patients with heart failure with reduced ejection fraction (HFrEF).[1]

Although the study drug was digitoxin, not its more commonly used congener digoxin, and it is no longer available in the United States, it can still be obtained in several countries in Europe and elsewhere.

Heart failure is a major public health problem, affecting more than 56 million people worldwide,[2] and its prevalence continues to rise. About 6.7 million Americans live with heart failure, which is responsible for 45% of cardiovascular deaths. An estimated 1 in 4 Americans will develop heart failure during their lifetime, and its prevalence is projected to reach 11.4 million cases by 2050.[3]

Despite advances in treatment, the mortality rate in patients with heart failure remains about 50% at 5 years.[2] This high residual risk is spurring research into the management of heart failure. In this context, and almost 3 decades after the last trial of a digitalis drug, the recent trial reopens the debate on the usefulness of digitalis therapy in heart failure.

This article reviews the Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF trial),[1] including its background, design, results, and implications in managing HFrEF.

**TABLE 1**
**Pharmacokinetic differences between digitoxin and digoxin**

| | Digitoxin | Digoxin |
|---|---|---|
| **Bioavailability** | > 90% | 60%–80% |
| **Plasma protein binding** | > 90% | 25% |
| **Tissue distribution** | 4–10 hours | 6–8 hours |
| **Volume of distribution** | 0.4–0.7 L/kg | 6–7 L/kg |
| **Metabolism** | Hepatic cytochrome P-450 (CYP3A) | Hepatic (only 16% of digoxin)<br>Not dependent on cytochrome P-450 |
| **Elimination** | 60% renal (conjugated metabolites)<br>40% biliary | 50%–70% excreted unchanged in urine<br>25%–28% extrarenal routes |
| **Half life** | 3–10 days | 1.5–2 days |

Based on information from references 9–11,13.

## BACKGROUND

Digitalis preparations have been used to treat heart failure for more than 2 centuries, first in the form of the leaves of the foxglove plants *Digitalis purpurea* and *Digitalis lanata*, and later as the cardiac glycosides digoxin and digitoxin.[4]

The pivotal Digitalis Investigation Group (DIG) trial,[5] published in 1997, showed that digoxin reduced hospitalizations for heart failure but had no impact on overall survival. Following these results, clinical guidelines recommended digoxin for heart failure, although its efficacy and safety remained debated.[6] Worse, meta-analyses of observational studies have suggested a possible association between its use and increased all-cause and cardiovascular mortality.[7]

As other treatments for HFrEF have been introduced, the role of digitalis compounds has diminished, shifting from the basis of treatment to a complementary role.[8]

Historically, digoxin has been the most commonly used digitalis agent, being widely available, approved by the US Food and Drug Administration,[9] and backed by extensive clinical evidence, while digitoxin lacked clinical trials to support its use. Although digitoxin is not currently marketed in the United States, it remains available in some regions of Europe.[1,10]

### How digoxin and digitoxin differ

Digoxin ($C_{41}H_{64}O_{14}$) and digitoxin ($C_{41}H_{64}O_{13}$) are nearly identical in their chemical structures, the difference being that digoxin has a hydroxyl (oxygen-hydrogen) group at a position where digitoxin has only a hydrogen atom.[11,12]

Although the mechanism of action is the same, this subtle difference in structure makes digitoxin more lipophilic, thereby altering its pharmacokinetics (**Table 1**).[9–11,13] It has greater bioavailability, greater plasma protein binding, and a longer half-life, which contribute to more stable plasma levels. In addition, whereas digoxin is mostly excreted unchanged in the kidneys, digitoxin undergoes hepatic metabolism and significant biliary excretion, which may make it safer in patients with renal disease.[13]

Another relevant difference between the drugs is their interaction with P-glycoprotein (P-gp), an active membrane transport protein. Digoxin depends heavily on P-gp for its absorption and elimination; therefore, drugs that modify P-gp such as verapamil, amiodarone, and propafenone, which are commonly used in cardiology, can significantly alter its plasma concentration.[12,13] In contrast, digitoxin, which is more lipophilic, is less dependent on P-gp and relies more on passive diffusion to cross biological membranes.[14]

## DIGIT-HF DESIGN

DIGIT-HF was an international, phase 4, multicenter, randomized, double-blind, placebo-controlled trial evaluating digitoxin added to guideline-directed medical therapy in HFrEF. It was conducted at 65 centers in Austria, Germany, and Serbia, and funded by the German Federal Ministry of Research, Technology, and Space.[1]

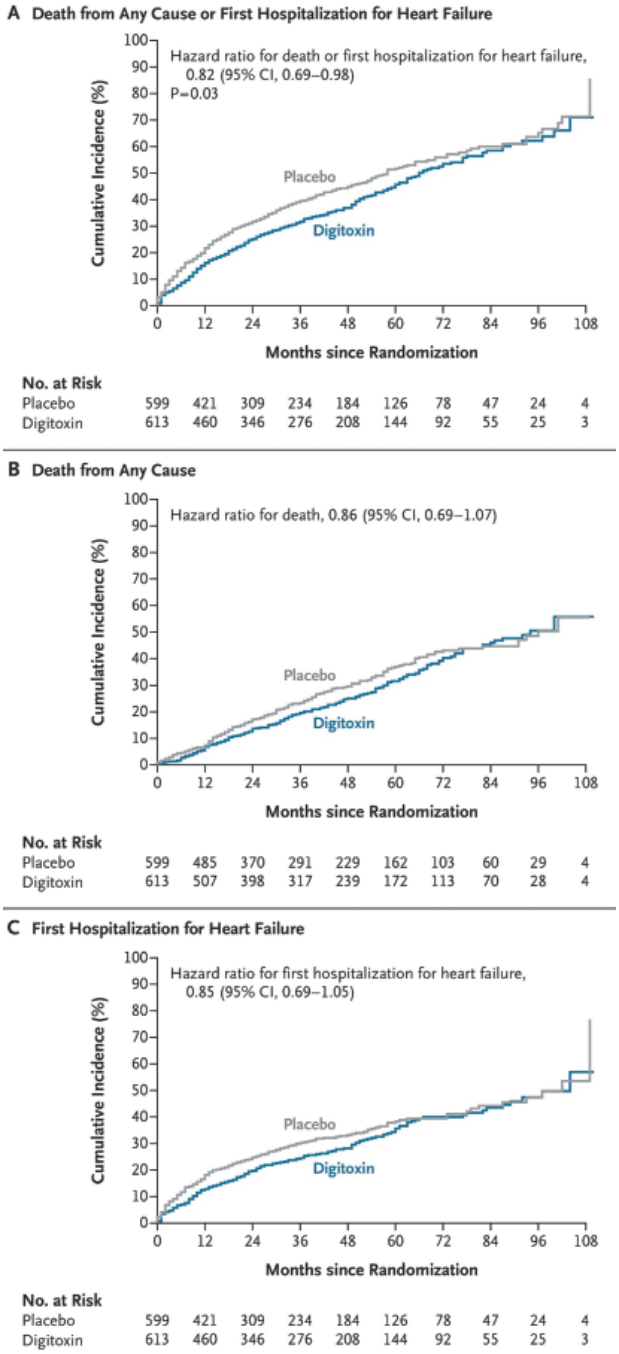



**Figure 1.** Cardiovascular outcomes in the Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF) trial.

CI = confidence interval

From Bavendiek U, Großhennig A, Schwab J, et al. Digitoxin in patients with heart failure and reduced ejection fraction. N Engl J Med 2025; 393(12): 1155–1165. doi:10.1056/NEJMoa2415471. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. License No. 6139170247864.

## Inclusion and exclusion criteria and digitoxin therapy

Patients could be included if they were age 18 years or older, had heart failure, were receiving guideline-directed medical therapy, were in clinically stable condition for at least 6 months before randomization, and had either of the following:

- Left ventricular ejection fraction 40% or less and were in New York Heart Association functional class III or IV, or
- Left ventricular ejection fraction 30% or less and were in New York Heart Association functional class II.[15]

The exclusion criteria included conditions that could increase the risk of toxicity or interfere with the interpretation of efficacy and safety, including bradyarrhythmias, electrolyte imbalances, acute coronary syndrome, recent coronary revascularization, unstable heart failure, and severe noncardiac comorbidities that limited survival.[15]

Participants were randomized in a 1:1 ratio to receive digitoxin or placebo. Digitoxin was started at 0.07 mg/day, and the serum level was measured once after 6 weeks to adjust the dose and maintain the serum concentration in the range of 8 to 18 ng/mL.[1]

## End points and statistical analysis

The primary outcome was a composite of death from any cause or hospitalization for worsening heart failure, whichever occurred first. The key secondary outcome combined death from any cause and any hospitalization for heart failure during follow-up. Additional secondary outcomes included cardiovascular mortality, death from heart failure, sudden cardiac death, noncardiovascular death, and all hospitalizations, both cardiovascular and noncardiovascular.[15]

The trial was designed to detect an absolute difference of 5% between groups in the primary outcome, with an expected incidence of 26% in the digitoxin group and 31% in the control group. The planned sample size was 2,190 patients with 734 events over a 36-month recruitment period and up to 48 months of follow-up.[1]

The primary analysis was by intention-to-treat. Two main hypotheses were tested:

- Digitoxin would be superior to placebo in terms of the primary outcome, and
- Digitoxin would not be inferior in terms of mortality (to rule out a possible harmful effect of digitoxin).[1]

**TABLE 2**
**Key findings from Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF) trial**

| | Digitoxin group (n = 613) | Placebo group (n = 599) | Hazard or rate ratio (95% confidence interval) |
|---|---|---|---|
| **Primary composite outcome** (death from any cause or first hospitalization for heart failure) | 39.5% | 44.1% | 0.82 (0.69–0.98) |
| Death from any cause | 27.2% | 29.5% | 0.86 (0.69–1.07) |
| First hospitalization for heart failure | 28.1% | 30.4% | 0.85 (0.69–1.05) |
| **Key secondary outcome** (death from any cause and hospitalization for heart failure) | 537 events | 531 events | 0.85 (0.67–1.09) |
| **Select subgroup analyses (statistically significant results)** | | | |
| Ejection fraction < 30% | 40.3% | 46.8% | 0.77 (0.59–0.99) |
| Nonischemic heart failure | 34.0% | 42.2% | 0.70 (0.53–0.93) |
| Heart rate ≥ 75 bpm | 42.0% | 48.2% | 0.63 (0.48–0.83) |
| Systolic blood pressure ≤ 120 mm Hg | 39.6% | 49.3% | 0.61 (0.48–0.79) |
| Body mass index < 30 kg/m$^2$ | 38.0% | 46.1% | 0.74 (0.58–0.93) |
| No hypertension | 26.4% | 40.3% | 0.57 (0.34–0.93) |
| No diabetes | 34.9% | 42.8% | 0.76 (0.60–0.96) |
| Estimated glomerular filtration rate ≤ 60 mL/min/1.73 m$^2$ | 50.2% | 55.3% | 0.73 (0.56–0.94) |
| No implantable cardioverter–defibrillator therapy | 31.8% | 43.2% | 0.57 (0.41–0.80) |
| No cardiac-resynchronization therapy | 35.0% | 43.7% | 0.72 (0.58–0.90) |

Based on information from reference 1.

## DIGIT-HF RESULTS

### Population

Between May 2015 and September 2023, 1,240 patients were randomized, of whom 1,212 were included in the analysis, with 613 in the digitoxin group and 599 in the placebo group.[1]

The mean age of the participants was 66 years, and 20.4% were women. Most had advanced heart failure: 70.4% were in New York Heart Association functional class III or IV, and their mean left ventricular ejection fraction was 29%. In addition, 27.2% had atrial fibrillation.

Regarding guideline-directed medical therapy, 95.7% of the patients were receiving a beta-blocker, 36.0% were receiving an angiotensin-converting enzyme inhibitor, 18.8% were receiving an angiotensin II receptor blocker, 39.5% were receiving an angiotensin receptor-neprilysin inhibitor, 76.2% were receiving a mineralocorticoid receptor antagonist, and 19.3% were receiving a sodium-glucose cotransporter 2 inhibitor. Regarding device therapies, 64.3% had an implantable cardioverter-defibrillator and 25.2% had received cardiac resynchronization therapy.[16]

### Impact on end points

Over a median follow-up of 36 months, the primary outcome occurred in 39.5% of patients in the digitoxin group, compared with 44.1% in the placebo group (hazard ratio [HR] 0.82, 95% confidence interval 0.69–0.98, $P = .03$). Thus, 22 patients needed to be treated with digitoxin to prevent 1 primary outcome event. However, neither the all-cause mortality rate nor the rate of first hospitalizations (the components of the composite outcome) was statistically different between groups (**Figure 1** and **Table 2**).[1]

**TABLE 3**
**Comparison of main findings from DIGIT-HF and other contemporary clinical trials in heart failure with reduced ejection fraction**

| Trial | Study drug[a] | Primary outcome | Hazard ratio (95% confidence interval) | Number needed to treat | Effect on mortality? |
|---|---|---|---|---|---|
| **DIGIT-HF**[1] | Digitoxin | Death or first hospitalization for heart failure | 0.82 (0.69–0.98) | 22 | No |
| **PARADIGM-HF**[17] | Sacubitril-valsartan | Cardiovascular death or first hospitalization for heart failure | 0.80 (0.73–0.87) | 21 | Yes |
| **DAPA-HF**[18] | Dapagliflozin | Cardiovascular death or worsening heart failure | 0.74 (0.65–0.85) | 20 | Yes |
| **EMPEROR-Reduced**[19] | Empagliflozin | Cardiovascular death or hospitalization for worsening heart failure | 0.75 (0.65–0.86) | 19 | No |
| **VICTOR**[20] | Vericiguat | Cardiovascular death or first hospitalization for heart failure | 0.93 (0.83–1.04) | 91[b] | Yes[b] |

[a]Digitoxin is a cardiac glycoside, sacubitril-valsartan is a combination neprilysin inhibitor and angiotensin II receptor blocker, dapagliflozin and empagliflozin are sodium-glucose cotransporter 2 inhibitors, and vericiguat is a soluble guanylate cyclase stimulator.
[b]The primary outcome was not statistically significant, and all-cause mortality was an exploratory outcome.

DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DIGIT-HF = Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction; PARADIGM-HF = Prospective Comparison of ARNI to Determine Impact on Global Mortality and Morbidity in Heart Failure; VICTOR = Vericiguat in Adults With Chronic Heart Failure and Reduced Ejection Fraction

The all-cause mortality rate was 27.2% in the digitoxin group and 29.5% in the placebo group (HR 0.86, 95% confidence interval 0.69–1.07), satisfying the prespecified noninferiority condition (HR < 1.303). No significant differences were observed in the other secondary outcomes.[1]

**Subgroup analysis** of the primary outcome showed positive trends in nearly all subgroups, but the results were statistically significantly better with digitoxin only in the following subgroups:

- Ejection fraction less than 30%
- Nonischemic heart failure
- Heart rate 75 beats per minute or higher
- Systolic blood pressure 120 mm Hg or lower (Those with higher systolic pressure actually had a slightly higher rate with digitoxin, but it was not statistically significant.)
- Body mass index 30 kg/m$^2$ or lower
- No hypertension
- No diabetes
- Estimated glomerular filtration rate 60 mL/min/1.73 m$^2$ or lower
- Without advanced devices.

### Safety

At least 1 serious adverse event was recorded in 29 patients (4.7%) in the digitoxin group and in 17 (2.8%) in the placebo group, including cardiac disorders in 3.4% and 1.8%, respectively.

Digitoxin or placebo was discontinued due to an adverse event in 56 patients (9.1%) in the digitoxin group and 61 (10.2%) in the control group.[1]

## STRENGTHS OF THE TRIAL

### Novelty and design

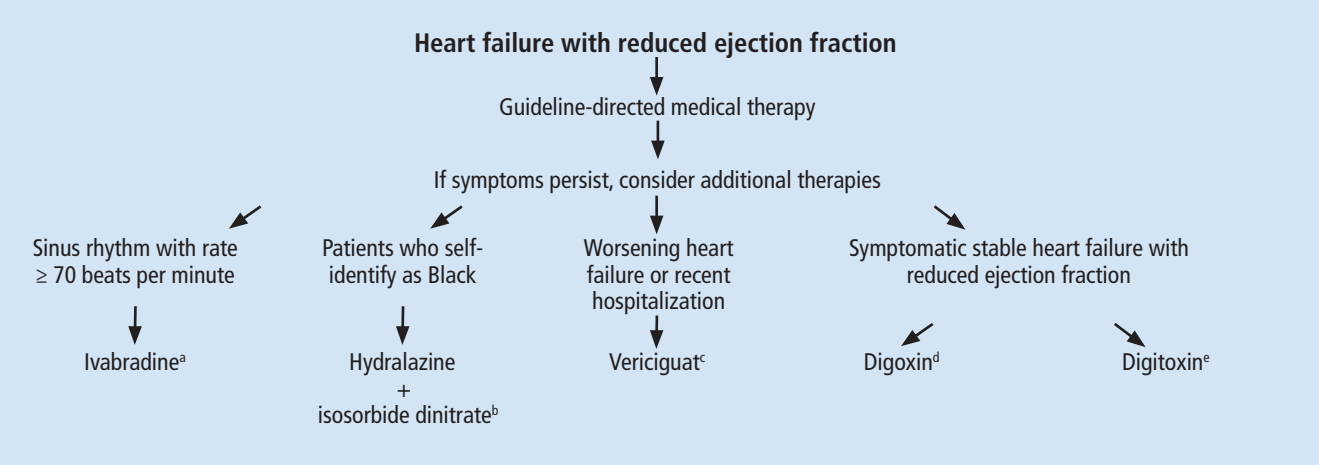
DIGIT-HF is the first trial to evaluate a digitalis drug since the DIG trial.[1,8] The use of digitoxin, whose benefit was uncertain, stands out as its main novelty. It was not sponsored by a pharmaceutical corporation, and it evaluated a drug that costs much less than most recent therapies for heart failure.[15]

### Meaningful population

DIGIT-HF enrolled a cohort of patients with advanced HFrEF and a high symptom burden. This group was underrepresented in other contemporary clinical trials in heart failure.[17–20] However, in a population with advanced heart failure, we would have expected more events and more deaths.

### Simple protocol

The authors used a simple digitoxin dosing protocol, with a single level measurement at 6 weeks to adjust




[a]Class 2a recommendation; decreased heart failure hospitalization and cardiovascular death.[26,27]

[b]Class 2a recommendation; decreased heart failure hospitalization and death.[26]

[c]Class 2b recommendation; decreased heart failure hospitalizations or cardiovascular death.[20,26,27]

[d]Class 2b recommendation; decreased heart failure hospitalizations.[26,27]

[e]May be considered as an adjunctive therapy for patients with symptomatic and stable heart failure with reduced ejection fraction despite optimized guideline-directed medical therapy; decreased death or first heart failure hospitalizations in the Digitoxin to Improve Outcomes in Patients With Advanced Chronic Heart Failure (DIGIT-HF) trial.[1]

**Figure 2.** Integration of digitoxin in treatment of heart failure with reduced ejection fraction.

Based on information from references 1, 26, and 27.

the dose.[15] This contrasts with the complex management of digoxin, which requires frequent monitoring of blood levels.[13]

After measurement, 58% of patients continued on the same dose, and 34% required a dose reduction.[1] Dose reduction was mainly associated with female sex, age 75 years and older, estimated glomerular filtration rate less than 50 mL/min/1.73 m², and body mass index less than 27 kg/m²; in such patients, an initial dose of 0.05 mg/day may be reasonable.[21]

### Clinical applicability and impact

Patient selection was based exclusively on clinical characteristics, without the need for biomarkers or complex tests, making it applicable in real-world practice.[15] Even in patients with advanced disease on guideline-directed medical therapy and with a high rate of device therapy, in whom the incremental benefit of a new therapy may be marginal, digitoxin offers a relevant additive effect, with a number needed to treat of 22, comparable to that in trials of newer drugs (**Table 3**).[1,16,21]

### Efficacy in relevant subgroups

Subgroup analysis suggests the benefit of digitoxin is maintained in patients with elevated heart rates, low systolic blood pressure, and renal disease, which are highly prevalent in patients with advanced heart failure who often cannot tolerate guideline-directed medical therapy.[1]

### Safety

The rate of serious adverse events was low, and discontinuation of treatment due to these events was similar across all groups. No signs of unexpected toxicity were detected, nor was there any increase in mortality attributable to digitoxin.[1] These findings contrast with historical concerns about the safety of digitalis compounds.[7,8,22] Consistent with the post hoc analyses of DIG, DIGIT-HF suggests that digitalis compounds are beneficial at low concentrations.[22–24]

## LIMITATIONS OF THE TRIAL

### Population and underrepresented subgroups

The trial was conducted in an exclusively European population, with fewer women (20%) and fewer patients with atrial fibrillation than in comparable trials.[16] These characteristics partially restrict the generalizability of the results.

### Unblinding and performance bias

Unblinding occurred in a limited number of cases (54 in the digitoxin group, 28 in the placebo group).[1] However, the relatively low number limits its overall impact and bias risk.

### Lower recruitment and rate of events than expected

DIGIT-HF, with 1,212 patients and 506 events, did not meet the planned sample size or event rate.[1] This reduced the study's statistical power and limited its ability to detect differences with treatment. The inclusion rate was 2.4 patients per center per year, which was well below usual practice. Recruitment had to be extended from 36 to 84 months, the planned interim analysis could not be performed, and the protocol had to be amended, all of which may have introduced additional biases and warrant cautious interpretation.[25]

These limitations should be viewed in the context of contemporary guideline-directed medical therapy, particularly following the approval of sodium-glucose cotransporter 2 inhibitors, which significantly reduce heart failure hospitalizations.[18,19] Compared with previous trials, DIGIT-HF included one of the largest populations receiving guideline-directed medical therapy.

### Significant composite outcome, nonsignificant individual components

The reduction in statistical power was probably part of the reason that although the primary composite outcome reached statistical significance, none of its components did when analyzed separately. However, effects for the components were directionally consistent with the overall result. Secondary outcomes were also not statistically significant.[1]

### Discontinuation rate and losses

Treatment was discontinued for reasons other than death in 58.9% of the digitoxin group and 55.1% with placebo.[1] This high discontinuation rate can dilute treatment effects. Although the intention-to-treat analysis partially mitigates this problem, the actual benefit may be underestimated in patients who stay on the drug. The authors do not specify clear reasons for these high discontinuation rates.

### Absence of functional parameters and quality of life

Mortality and readmissions are not the only essential factors in heart failure. Other parameters, such as quality-of-life tests, the 6-minute walk test, or the N-terminal probrain natriuretic peptide (NT-proBNP) level, could strengthen the potential benefits of digitoxin and would have allowed us to compare DIGIT-HF with the most recent heart failure trials.

## TRANSLATING DIGIT-HF TO EVERYDAY PRACTICE

Digoxin carries a class 2b (weak) recommendation, level of evidence B (moderate) for patients with HFrEF whose symptoms persist despite guideline-directed medical therapy in guidelines from the American College of Cardiology and the European Society of Cardiology.[26,27] In this same setting, digitoxin offers an additional benefit by reducing the risk of death or first hospitalization for heart failure in patients with symptomatic HFrEF despite guideline-directed medical therapy.[1]

Other therapies complementary to guideline-directed medical therapy, such as ivabradine (which has a 2a recommendation) or vericiguat (2b recommendation), can help selected patients, but each has practical limitations. Ivabradine is ineffective in patients with atrial fibrillation and is only indicated if the heart rate is higher than 70 beats per minute despite optimal use of beta-blockers.[26,27] Vericiguat, for patients with recent worsening, may be limited by hypotension, and its benefit appears to diminish with very high levels of NT-proBNP.[26,27]

Given these limitations, digitoxin might be considered an additional option. **Figure 2** summarizes a potential new therapeutic approach if the benefits of digitoxin are confirmed in the near future.[1,20,26,27]

Finally, given its inotropic properties, neurohormonal effects, and pharmacokinetic profile, digitoxin may benefit patients who cannot tolerate guideline-directed medical therapy because of hypotension or worsening renal function, common problems in real-world clinical practice.[1,10,21]

## UNANSWERED QUESTIONS

DIGIT-HF brings digitoxin back into the field of heart failure care. But questions remain:

**Is digitoxin better than digoxin?** The 2 drugs have never been directly compared, and lacking such a trial, the DIGIT-HF results cannot be extrapolated to other digitalis compounds.[1]

**Does digitoxin truly benefit all subgroups?** Although the benefit of digitoxin was consistent across subgroups, the study lacked sufficient statistical power to confirm these findings in all subgroups, leaving uncertainty in specific populations.[1]

**Is digitoxin truly safe?** Although low in absolute terms, the incidence of serious adverse events was higher in the digitoxin group.[1] Further research is needed to define its safety profile, especially in patients with comorbidities.

**Does digitoxin offer an advantage in patients with atrial fibrillation?** Given evidence suggesting

that beta-blockers are more beneficial in patients with HFrEF who are in sinus rhythm than in those with atrial fibrillation,[28,29] digitoxin may offer an opportunity in the latter group, especially if they have serious symptoms. This hypothesis will need to be shown in future studies.

## FUTURE IMPLICATIONS

The good results from DIGIT-HF are exciting. Following DIGIT-HF, digitoxin might be considered in future guidelines, alongside digoxin. Furthermore, its use is expected to increase in countries where it is available. Its low cost also makes market entry in other countries plausible. However, we need more evidence from clinical trials and real-world experience regarding the use of digitoxin in routine clinical practice.

The DECISION trial (Digoxin Evaluation in Chronic Heart Failure: Investigational Study in Outpatients in the Netherlands),[30] testing low-dose digoxin in heart failure, is ongoing. This evidence will contribute to defining more precisely the role of digitalis in the current treatment of heart failure.

## DISCLOSURES

Dr. Solé-González disclosed teaching and speaking for Bayer and Novartis and other activities from which remuneration is received or expected for Rovi. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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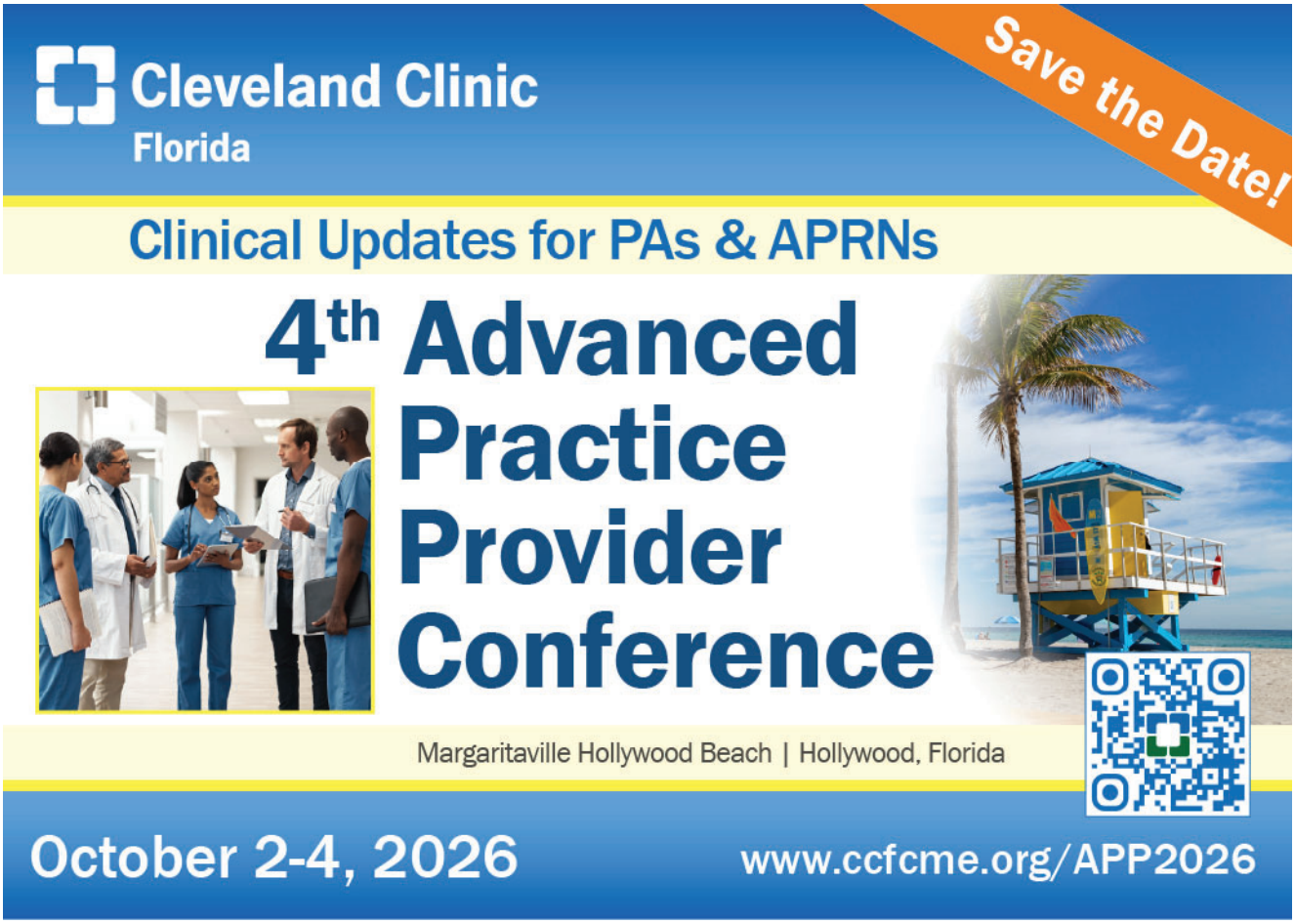
***Address:*** *Enmanuel A. Leiva-Murillo, MD, Department of Internal Medicine, Hospital Clínic, Carrer de Villarroel, 170, L'Eixample, 08036 Barcelona, Spain; ealeiva@clinic.cat*



REVIEW

**Nicholas Salupo, DO**
Ohio University Heritage College of Osteopathic Medicine, Athens, OH; Dayton Kidney, Dayton, OH

**Korey Bartolomeo, DO**
Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH

**Elias Bassil, MD**
Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

**Corey Cavanaugh, DO**
Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH, Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

**Georges Nakhoul, MD, MEd**
Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

**Jonathan Taliercio, DO**
Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

**Ali Mehdi, MD, MEd**
Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Complement inhibition: A whole new world

## ABSTRACT

The complement system is a central component of the innate immune system, and it is a bridge to the adaptive immune system. With this broad functional reach, dysregulation of this system contributes to a wide range of inflammatory and autoimmune conditions. Drugs that inhibit the complement system have dramatically improved outcomes in many previously untreatable diseases, and the number of approved indications is growing rapidly, requiring specialists and generalists alike to be familiar with these drugs.

## KEY POINTS

Complement is critical for proper immune surveillance and activation of the immune response.

Chronic, inappropriate, and uncontrolled complement activation can be associated with inflammatory diseases.

Complement inhibitors are already used in many medical specialties, and their indications are rapidly expanding. As these treatments become more common, clinicians will need to be acquainted with their indications and side effects.

Complement inhibitors increase the risk of infections with encapsulated organisms, particularly meningococci, requiring close monitoring, vaccinations, and prophylactic antibiotics.

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The complement system, like the Krebs cycle, is something many physicians studied in school and then quickly forgot because it had limited clinical relevance in routine practice. However, as our understanding of the pathophysiologic basis of diseases has advanced, the roles of the complement system's various elements have become more apparent across a wide spectrum of diseases.

*See related editorial, page 237*

In the past few years, several complement inhibitors have received US Food and Drug Administration (FDA) approval for a variety of indications, reshaping management algorithms for numerous diseases. As these medications enter the mainstream and with more on the way, understanding the complement system and the benefits and risks of therapeutic blockade has become crucial for optimal patient care.

Here, we provide a brief overview of the complement system and its role in the pathophysiology of a variety of diseases. We then highlight how complement inhibition has emerged as a revolutionary therapeutic strategy with current and future FDA approvals. We finally discuss important considerations for patients receiving these drugs, emphasizing the risk of infections.

## OLD DISEASES, NEW THERAPEUTIC HORIZONS

*A 31-year-old man who has been healthy until now is being evaluated for microscopic hematuria and proteinuria. His estimated glomerular filtration rate is 83 mL/min/m$^2$, indicating stage 2 chronic kidney*

*disease. Urine sediment analysis reveals dysmorphic red blood cells, and his urine protein-to-creatinine ratio is elevated at 1.5 g/g. Immune serologic workup is unrevealing, including normal C3 and C4 levels.*

*He undergoes a kidney biopsy, which shows mesangial hypercellularity in most sampled glomeruli, focal endocapillary hypercellularity, and segmental glomerulosclerosis in 2 glomeruli. One glomerular crescent is also seen. Tubular atrophy and interstitial fibrosis are minimal. Immunofluorescence reveals intense mesangial immunoglobulin (Ig) A and C3 staining.*

This is a classic case of IgA nephropathy with predominantly inflammatory lesions on the kidney biopsy. Until recently, the only immunomodulatory options for treating it were systemic glucocorticoids, for which trials showed variable efficacy but an unequivocally increased risk of infections and death. Given the uncertain risks and benefits of steroids, treatment of IgA nephropathy varied: some clinicians gave them, others didn't, giving only nonimmunomodulatory, antiproteinuric drugs such as renin-angiotensin-aldosterone system inhibitors and sodium-glucose cotransporter 2 inhibitors, particularly for patients who had preserved kidney function without nephrotic syndrome.

Neither of these approaches was wrong, given the limited options at the time! The 2021 Kidney Disease Improving Global Outcomes guideline,[1] currently undergoing a much-needed update with other recently approved medications, supported both approaches and emphasized careful patient selection and risk-benefit discussion when contemplating systemic steroid therapy for IgA nephropathy.

IgA nephropathy is but one of many inflammatory diseases that had limited therapeutic options, while progressive damage accrued over years of uncontrolled disease.[2] Experts would advocate for immunomodulatory therapy in such scenarios if a safe and effective option was available. Until recently, such an option was not available, but fortunately, things are rapidly changing.

Complement inhibitors have been a major breakthrough, offering an effective steroid-sparing approach for patients with inflammatory disease. In the past 3 years alone, 3 medications received FDA approval for treating IgA nephropathy, and many more are on the horizon. Iptacopan, a factor B inhibitor, backed by promising efficacy and safety data, received accelerated FDA approval for IgA nephropathy in late 2023.[3]

In this review, we do not aim to do a deep dive into the pathophysiology and management of IgA nephropathy, or any of the other renal or nonrenal conditions in which complement-inhibiting therapy is currently used. Instead, we hope to highlight the previously underappreciated and unrecognized role of the complement system in many diseases and how complement inhibitors can revolutionize (and in some cases already have revolutionized) their management.

## THREE PATHWAYS THAT CONVERGE ON C3 AND THEN C5

Our understanding of the complement system has advanced tremendously since complement was first described in the 19th century as a heat-labile factor that complemented the function of a heat-stable factor (antibodies), although the terms *complement* and *antibodies* would not be coined until many years after.[4,5] Over 50 unique proteins have been identified in the complement cascade.

Complement is a surveillance mechanism, constantly keeping watch against a broad array of "foreign" threats, nonspecifically labeling them, engaging effector immune cells, and recruiting additional complement proteins to eliminate said threats.[6] Thus, it has canonical functions in the innate immune system and in mediating adaptive immune system activation. It also has noncanonical functions that are beyond the scope of this review.

Complement activation can occur via any of 3 pathways (**Figure 1**):

- Targeted recognition of antibodies (IgG or IgM) in the classical pathway
- Direct recognition of pathogen-associated molecular patterns in the lectin pathway
- Spontaneous activity in the alternative pathway.

All 3 pathways converge and culminate in production of C3 convertase, an enzyme that cleaves the propeptide C3 into immunologically active C3a (an anaphylatoxin with pro- and anti-inflammatory properties) and C3b products. C3b has numerous roles including opsonization of foreign pathogens and native cells (ie, tagging them for destruction by phagocytes), priming the adaptive system, and generating additional complement. For instance, C3b binding to C3 serves as substrate for further alternative-pathway generation of C3 convertase, while binding of C3b to C3 convertase generates C5 convertase.

Terminal complement activation results from C5 convertase cleaving C5 into C5a, a largely proinflammatory anaphylatoxin, and C5b. C5b binds C6 and C7 in the fluid phase before associating with the target membrane, then recruits C8 and triggers C9 polymerization in the plasma membrane. This forms the basis of the pore-forming membrane attack complex (MAC, or C5b-9) to facilitate osmotic lysis of cells and pathogens.

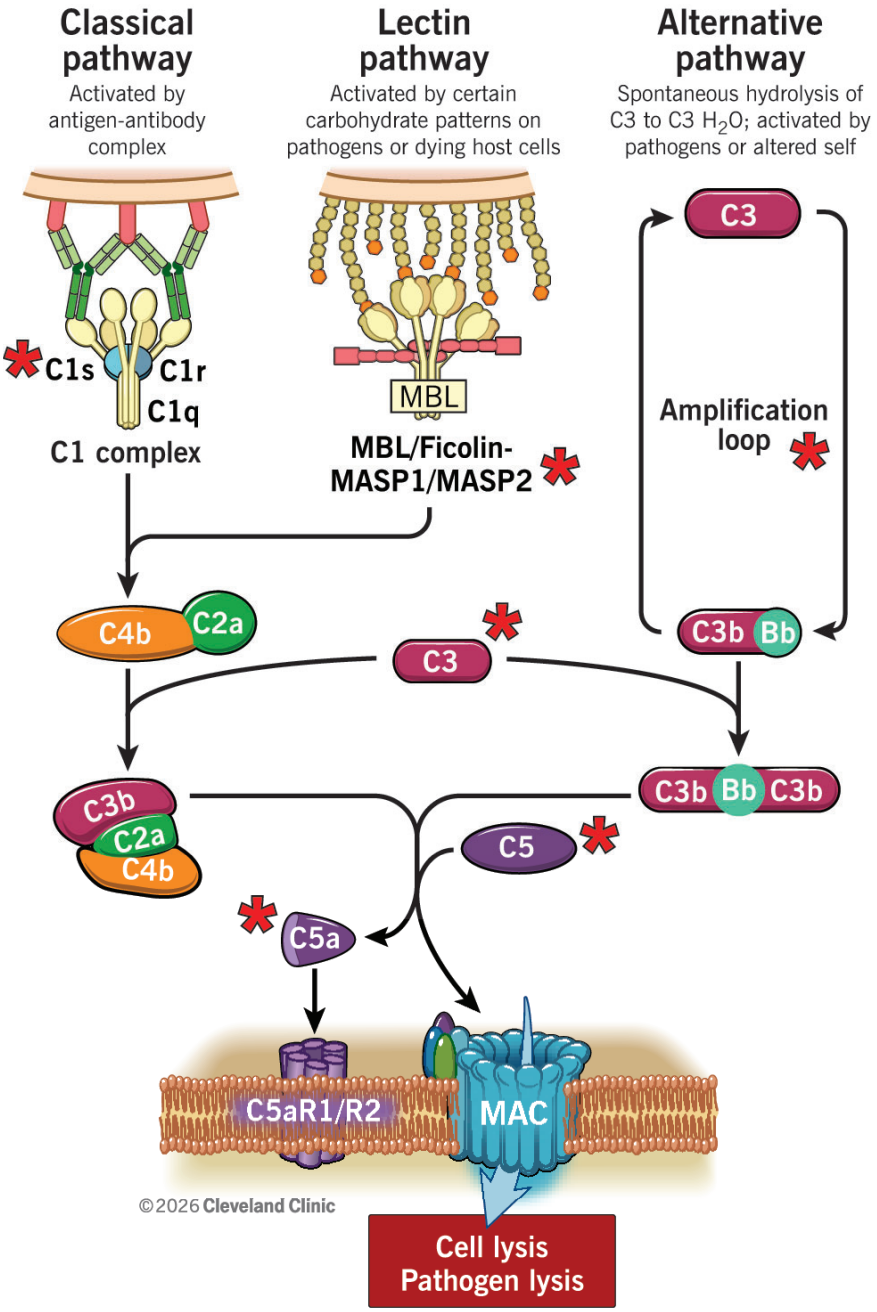


**Figure 1.** Complexities in complement activation open opportunities for therapeutic inhibition. Activation of complement occurs in response to a diverse range of triggers, leading to formation of different isoforms of C3 convertase (C4bC2a in the classical and lectin pathways, C3bBb in the alternative pathway). C3 convertases catalyze cleavage of C3 to products that lead to formation of C5 convertase (C4bC2aC3b in the classical and lectin pathways, C3bBbC3b in the alternative pathway) and eventually terminal complement activation, most commonly characterized by formation of the membrane attack complex (MAC, or C5b-9). Drug development has focused on a number of these steps (designated by red asterisks) in an attempt to refine regulation in certain pathologies. See the article text for more details.

MBL = mannose-binding lectin; MASP1 = mannan-binding lectin–associated serine protease 1; MASP2 = mannan-binding lectin–associated serine protease 2; C5aR = C5a receptor

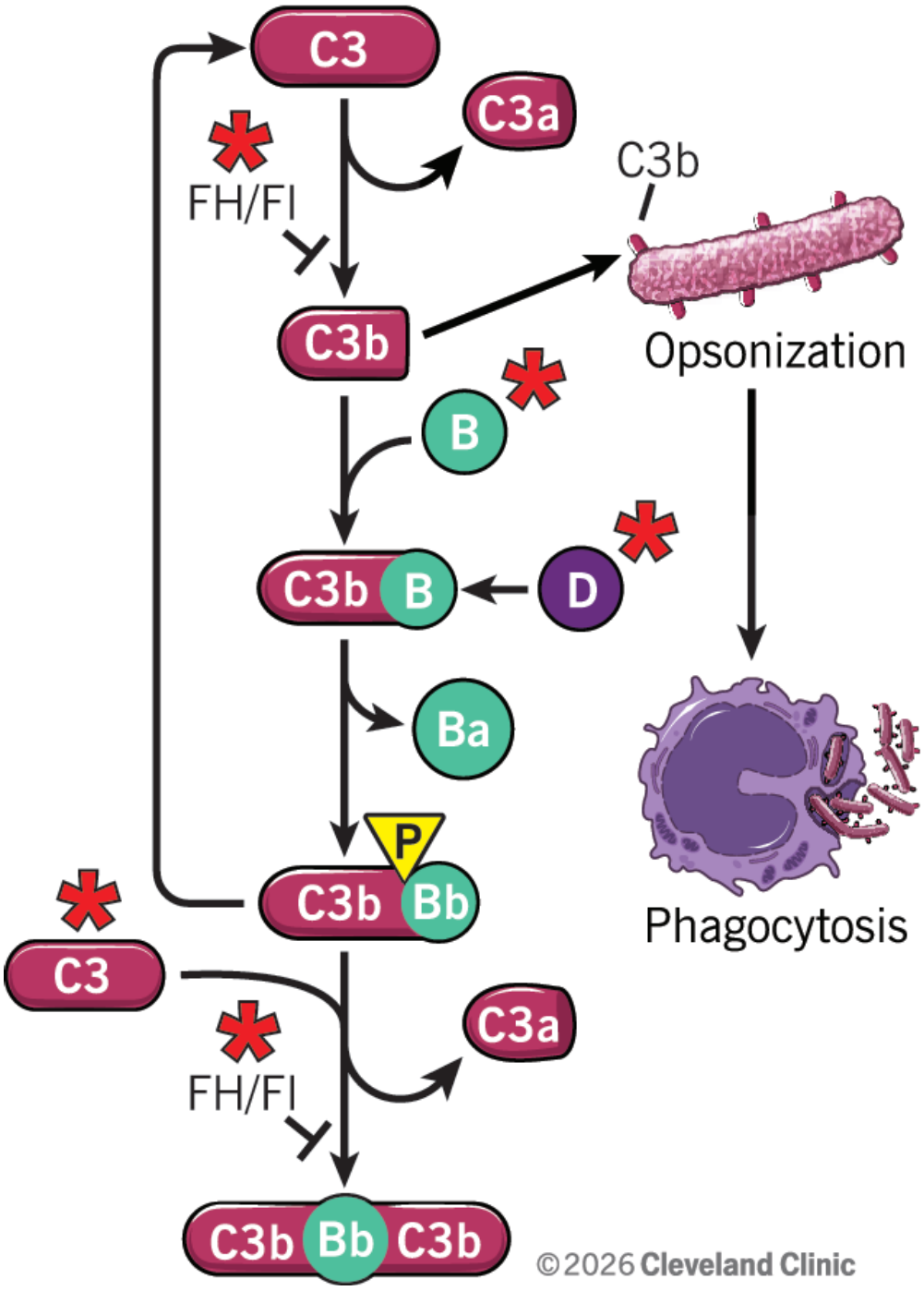


**Figure 2.** The alternative pathway drives amplification of complement activation. C3b generated from any activating pathway recognizes circulating native C3, recruiting factor B (B) and factor D (D) to form the major C3 convertase C3bBb. Properdin (P) stabilizes this convertase, enabling sustained amplification of C3b generation as C3 convertase (C3bBb) cleaves more C3. Factor H (FH) and factor I (FI) act as physiologic regulators of this process to control the amplification process. Various components of this system are current or future targets for therapeutic intervention (designated by red asterisks).

**TABLE 1**
**Key components of the complement system**

| Component | Function |
|---|---|
| **Positive mediators** | |
| C3a[a] | Anaphylatoxin |
| C3b | Opsonizes microbes and noxious host cells |
| C3a receptor | C3a anaphylatoxin receptor |
| C5a | Anaphylatoxin |
| C5b | Initiates membrane attack complex formation |
| C5a receptor | C5a anaphylatoxin receptor |
| Membrane attack complex (C5b-9) | Consists of C5b, C6, C7, C8, and polymerized C9<br>Causes direct lytic killing of pathogens and noxious host cells by forming a pore that mediates cell lysis |
| Factor B | Serine protease that when cleaved to Bb forms the catalytic component of the alternative pathway C3 convertase |
| Factor D | Serine protease that cleaves factor B when bound to C3b |
| **Negative regulators** | |
| C1 inhibitor | Inhibits C1r, C1s, mannan-binding lectin–associated serine protease (MASP) 1, MASP2 |
| Factor I | Degrades C3b and C4b |
| Factor H | Factor I cofactor for C3b inhibition |
| C4b binding protein | Inhibits formation of C3 convertase in the classical and lectin pathways |
| Decay activating factor (CD55) | Accelerates decay of C3 and C5 convertases on cell surfaces |
| Membrane cofactor protein (CD46) | Cofactor for factor I–mediated degradation of C3b and C4b on host cells |

[a]Has both positive and negative regulatory effects.

Based on information from references 4 and 5.

Complement activation is a feed-forward system in which activated proteins directly contribute to activation of subsequent components, rapidly amplifying the response. This is particularly evident in the alternative pathway, as it provides low-level activation of complement products, allowing the body to constantly and nonspecifically stand guard, in a process known as "tick-over."[6]

Tick-over is believed to result from spontaneous hydrolysis of an internal thioester bond in C3, resulting in C3($H_2O$), which is recognized by circulating factor B, kicking off a series of protein interactions that result in the formation of an initial C3 convertase (C3[$H_2O$]Bb, sometimes called C3b-like C3 or iC3) to generate fluid-phase C3b.[7,8] As illustrated in **Figure 2**, C3b recognizes additional circulating native C3 and recruits factor B for formation of the major alternative pathway C3 convertase, C3bBb, leading to rapid upregulation of C3b products in an amplification loop.[6]

## NORMALLY, COMPLEMENT IS A BALANCED SYSTEM

A complex system maintains the balance of complement activation and inhibition (**Figure 2** and **Table 1**[4,5]), with enough activation to protect against foreign threats but enough regulation to prevent collateral damage to the host from uncontrolled activation. In this system, negative regulators of complement in the serum (fluid phase) and attached to the cell membrane limit complement activation by decreasing the generation of anaphylatoxins, dissociating C3b from host cells, or inhibiting assembly of MAC.[6]

Factor H is the main fluid-phase negative regulator of complement activation, working with factor I to prevent formation and limit the stability of C3 convertase in the alternative pathway (**Figure 2**),[6] while C4b-binding protein inhibits C3 convertase formation in the classical and lectin pathways.

**TABLE 2**
**Currently approved complement inhibitors**

| Drug | Therapeutic target | Indication |
|---|---|---|
| Eculizumab | Humanized monoclonal antibody against C5 | Paroxysmal nocturnal hemoglobinuria<br>Atypical hemolytic uremic syndrome<br>Neuromyelitis optica<br>Adult acetylcholine receptor antibody–positive generalized myasthenia gravis |
| Ravulizumab | Humanized monoclonal antibody against C5 | Paroxysmal nocturnal hemoglobinuria<br>Atypical hemolytic uremic syndrome<br>Adult acetylcholine receptor antibody–positive generalized myasthenia gravis |
| Crovalimab | Humanized monoclonal antibody against C5 | Paroxysmal nocturnal hemoglobinuria |
| Pegcetacoplan | Pegylated peptide that binds to C3 and C3b | Paroxysmal nocturnal hemoglobinuria<br>C3 glomerulopathy<br>Idiopathic membranoproliferative glomerulonephritis<br>Geographic atrophy secondary to age-related macular degeneration |
| Avacopan | Small-molecule inhibitor of the C5a receptor | Antineutrophil cytoplasmic antibody–associated vasculitis |
| Iptacopan | Small-molecule inhibitor of factor B | Paroxysmal nocturnal hemoglobinuria<br>Immunoglobulin A nephropathy<br>C3 glomerulopathy |
| Danicopan | Small-molecule inhibitor of factor D | Paroxysmal nocturnal hemoglobinuria (combined with a C5 inhibitor) |
| Sutimlimab | Humanized monoclonal antibody against C1s | Cold agglutinin disease |
| Zilucoplan | Macrocyclic peptide C5 inhibitor | Myasthenia gravis |
| Pozelimab | Humanized monoclonal antibody against C5 | CD55-deficient protein-losing enteropathy |
| Avacincaptad pegol | Pegylated RNA aptamer inhibiting C5 cleavage | Geographic atrophy |
| C1 esterase inhibitor | Recombinant serine protease inhibitor of C1 esterase | Hereditary angioedema |
| Vilobelimab | Chimeric monoclonal antibody against C5a | COVID-19 (emergency use authorization) |

In addition to these soluble regulators, several membrane-bound proteins protect host cells from complement-mediated injury. Decay-accelerating factor (CD55) destabilizes both C3 and C5 convertases on cell surfaces, while membrane cofactor protein (CD46) serves as a critical cofactor for factor I–mediated cleavage of C3b and C4b on host cells. Defects in these membrane regulators result in severe complement-mediated disease, exemplified by CD55 deficiency (CHAPLE syndrome, characterized by **c**omplement **h**yperactivation, **a**ngiopathic thrombosis, **p**rotein-**l**osing **e**nteropathy, and systemic inflammation).[9]

## COMPLEMENT DYSREGULATION IN MANY DISEASES

The balance between complement activation and inhibition is critical, as unregulated activation can damage host tissues, manifesting as a variety of diseases.

C3 glomerulopathies (C3 glomerulonephritis and dense deposit disease) are ultrarare but prototypic renal diseases in which complement dysregulation drives pathology.[10,11] Paroxysmal nocturnal hemoglobinuria and complement-mediated thrombotic microangiopathy, also known as atypical hemolytic uremic syndrome, are 2 hematologic (and sometimes renal-limited)

diseases where complement dysregulation is clearly pathogenic.[12–15] In complement-mediated thrombotic microangiopathy, around 60% of patients have underlying pathogenic genetic variants in complement and complement regulator proteins.[16]

Aside from these prototypic complement-mediated diseases, complement activation plays an important role in the pathophysiology of a multitude of other diseases, including IgA nephropathy, antineutrophil cytoplasmic antibody–associated vasculitis, age-related macular degeneration, myasthenia gravis, and neuromyelitis optica.[17–21] Management of these diseases has evolved over the past few years to include complement blockade at various levels.[22] Complement activation is also thought to play a role in many other conditions, including membranous nephropathy, lupus nephritis, idiopathic membranoproliferative glomerulonephritis, and antiphospholipid syndrome.[23]

Insights gained from studying complement involvement and inhibition in kidney diseases are increasingly relevant not just to hematology but to many other disciplines, highlighting complement as a shared pathogenic axis across specialties, and a very promising therapeutic target.

## COMPLEMENT INHIBITION AS TREATMENT

Given complement's involvement in the pathogenesis of an expanding list of diseases, complement inhibition has emerged as a therapeutic strategy.[24,25]

Blocking C3 and C5 was the most obvious avenue to pursue, given that all 3 complement pathways converge on C3 and then C5. Eculizumab, a humanized monoclonal antibody against C5, was the first complement inhibitor to be approved; it was approved for paroxysmal nocturnal hemoglobinuria in 2007 and then for atypical hemolytic uremic syndrome in 2011.[26] This paved the way for drugs targeting not only these downstream components (C3, C5) but also specific upstream components in the classical, alternative, and lectin pathways (factor B, factor D, mannan-binding lectin–associated serine protease [MASP] 2, C1s, C2). The soluble complement inhibitors factor H and factor I are also being used to attenuate complement activation.[27]

Some complement inhibitors are already approved for a variety of indications (**Table 2**), and many more are in advanced clinical trials. In addition, the science of complement blockade is evolving rapidly, with fusion proteins, products that silence RNA, and gene editing all on the horizon.[27]

## WHY THE EXCITEMENT ABOUT COMPLEMENT INHIBITORS?

### Better outcomes

Complement inhibitors have revolutionized the treatment of many diseases that used to be plagued with very poor outcomes. The courses of diseases like paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome are now significantly modified with C5 blockers, which achieve impressive response rates that were once unthinkable.[26,27] This led to these agents being used off-label, with variable success, in many other diseases including C3 glomerulopathy, antibody-mediated rejection, and hematopoietic stem cell–associated thrombotic microangiopathy.

But blocking C5 has not worked in all these diseases, likely in part because of the many ways complement affects the immune system. For example, a C5 inhibitor was ineffective in treating C3 glomerulopathy, while drugs that block the complement system further upstream (eg, at C3) showed much more success. Pegcetacoplan (a C3 blocker) and iptacopan (which inhibits factor B) are FDA approved for managing C3 glomerulopathy, with pegcetacoplan also revolutionizing the care of patients with geographic atrophy secondary to age-related macular degeneration.

### Less steroid use

Another major advantage of complement inhibitors is their steroid-sparing effect. Corticosteroids, while effective in many inflammatory conditions, have well-documented and significant side effects such as weight gain, hyperglycemia, osteoporosis, hypertension, and risk of infection. But now, patients with antineutrophil cytoplasmic antibody–associated vasculitis can get off steroids quicker if they receive avacopan, a C5a receptor inhibitor, without compromising response rates.[28] Patients with IgA nephropathy now have effective nonsteroidal, FDA-approved options with iptacopan and other agents.[9] This steroid-sparing effect is a huge win for our patients who have long suffered the long-term consequences of chronic and repeated steroid therapy.

In nephrology, many phase 2 and 3 trials are currently evaluating the efficacy of complement blockade in various diseases including membranous nephropathy, lupus nephritis, idiopathic membranoproliferative glomerulonephritis, diabetic kidney disease, and focal segmental glomerulosclerosis.[29] Excitingly, as complement plays a role in renal ischemia-reperfusion injury, complement inhibitors are also being studied to prevent delayed graft function after kidney transplantation and acute kidney injury following cardiac surgery.

**TABLE 3**
**Vaccination guidelines for patients on complement inhibitors**

| Vaccine | Serocoverage | Recommendations |
|---|---|---|
| **Pneumococcal** | | |
| Prevnar 20 (PCV20) | 20-valent | Give 1 dose of PCV20 **or** PCV21 at least 5 years after the most recent pneumococcal vaccination |
| Capvaxive (PCV21) | 21-valent | |
| **Meningococcal** | | |
| Menactra<br>Menveo<br>MenQuadfi | Serogroups A, C, W, and Y | Give 2 doses 8 weeks apart, and a booster every 5 years while on complement therapy |
| Bexsero<br>Trumenba | Serogroup B | Give 3 doses: at 0, 4–8 weeks, and 6 months; booster at 1 year after series completion then every 2–3 years while on complement therapy |
| ***Haemophilus influenzae*** | | Vaccinate if not previously vaccinated |

Based on information from reference 31.

Continued research is likely to expand the applications of complement inhibitors, making this class of medications a cornerstone in the management of many inflammatory disorders, and potentially more that have traditionally been considered noninflammatory, such as diabetic kidney disease and delayed graft function.

## RISK OF MENINGOCOCCAL INFECTIONS

Infections are the major concern for patients on complement therapy. Most of the recommendations regarding infections are derived from studies of the C5 monoclonal antibodies eculizumab and ravulizumab, which have undergone longer postmarket surveillance and testing in more patient populations.

The greatest concern with these terminal complement inhibitors is a risk of infections by encapsulated bacteria, especially life-threatening meningitis from *Neisseria* species. Although the absolute numbers are low (2–3 cases per 1,000 patient years), patients on these drugs have 1,000 to 2,000 times greater risk of meningococcal infections than the general population.[30] This risk remains high even with appropriate vaccination and antibiotic prophylaxis (**Table 3**).[31]

Vaccination against encapsulated bacteria, supported by recommendations from the US Centers for Disease Control and Prevention, should be given 2 weeks before starting complement inhibitors. Importantly, meningococcal vaccination against all meningococcal serotypes (A, C, W, Y, and B) is required.[31]

If a complement inhibitor needs to be started earlier than 2 weeks after vaccination, antibiotic prophylaxis with amoxicillin (or ciprofloxacin or a macrolide if the patient is allergic to penicillin) is required. How long to keep giving prophylactic antibiotics is not clear, but they are generally continued for at least 2 weeks after starting the vaccination series, and some experts recommend continuing them until the meningitis vaccinations are completed (6 months) or even for as long as the patient receives a complement inhibitor.[31]

Importantly, the FDA requires that clinicians and patients enroll in a risk evaluation and mitigation strategy program to help lower the risk of these serious infections. Given the complexity of vaccination schedules, antimicrobial prophylaxis, and evolving pathogen risks, multidisciplinary collaboration—including infectious disease expertise—is often beneficial when starting or monitoring complement inhibitor therapy.

Avacopan, a C5a receptor inhibitor, does not increase the risk of meningococcal infections, as it targets only C5a, the anaphylatoxin byproduct of C5 cleavages, leaving C5b intact to eventually form MAC. A major area of uncertainty is whether the infectious risk seen with older terminal complement inhibitors will be seen with pathway-specific complement blockers (factor B, factor D, MASP 2) or proximal complement blockers, such as C3 inhibitors. While no current evidence supports an increased risk of meningitis with non-C5 complement inhibitors, all patients in these clinical trials still received appropriate vaccination, given the theoretical risks.

We support current US Centers for Disease Control and Prevention guidance that all complement inhibitors be presumed to have similar infectious risks,[31] until longer-term data become available, considering the devastating consequences of infection and relative ease of reducing risk. Both patients and clinicians should be aware of these risks and the need for prompt evaluation and antibiotic therapy if such an infection is suspected. This not only includes the prescribing nephrologist, hematologist, or neurologist, but also the acute care clinicians at express clinics and emergency physicians, hospitalists, and intensivists.

Aside from the infectious concerns, these medications are reasonably well tolerated. Injection-site reactions are the most common side effects with injectable

formulations, usually consisting of mild hypersensitivity (pruritus, headache, nausea, dizziness), but they can rarely be associated with anaphylaxis. Patients must be monitored for at least 1 hour after drug administration.

Metabolic disturbances, including hypertension, hyperlipidemia, and hypokalemia, have been noted in clinical trials, as have adverse hepatic events. **Table 4** details medication-specific considerations.

## ARE COMPLEMENT INHIBITORS SAFE IN PREGNANCY?

Complement has been implicated in a variety of pathologic states in pregnancy. Complement-mediated thrombotic microangiopathy can be triggered in the peripartum period and is usually associated with other obstetric complications such as preeclampsia.[32] Interestingly, a 2025 study reported that variants in the terminal complement pathway genes *C5* and *C6* were associated with and may predispose to preeclampsia.[33]

Eculizumab, the complement inhibitor best studied in pregnancy, is a category C drug, as it can cross the placenta and reach low levels in neonates, but it has been used safely in pregnancy-associated complement-mediated thrombotic microangiopathy.[34]

Similarly, eculizumab does not seem to be excreted in breast milk and is likely to be safe with lactation. Data on safety during pregnancy and lactation are lacking for other terminal and proximal complement inhibitors. More formal recommendations are expected in the future as data accumulate regarding safety of these drugs in these at-risk populations.

## EXPENSIVE BUT WORTH IT?

Like other novel therapies, complement inhibitors are expensive, which becomes more relevant as many patients require extended therapy—sometimes lifelong! Even eculizumab biosimilars, soon to be on the market, are expected to have a high price tag. Cost-effectiveness analyses will be instrumental in the eventual accessibility and wider uptake of these effective therapeutic options.

Active areas of investigation include the optimal duration of complement inhibition and biomarkers to aid in monitoring recurrence of disease or therapeutic levels while on these medications.

## COMPLEMENT: A SYSTEM TO REMEMBER

The complement system plays a crucial role in immune function and is increasingly implicated in the pathogenesis of various diseases across disciplines. Complement blockade has emerged as a therapeutic approach, providing the only effective treatment for some diseases, and promising effective and safer options in others.

The list of available and approved medications is rapidly increasing, and we expect that most practitioners will soon begin encountering patients on them with problems that will require in-depth knowledge of these medications. Forgetting about complement is no longer an option in providing optimal patient care.

**TABLE 4**
**Noninfectious medication-specific considerations and adverse effects with complement inhibitors**

| Complement inhibitor | Considerations and adverse effects |
|---|---|
| **Avacopan** | Liver injury<br>Hypertension<br>Hypersensitivity reactions<br>Gastrointestinal disturbances (nausea, diarrhea) |
| **C5 inhibitors (eculizumab, ravulizumab)** | Infusion reactions<br>Headache<br>Hypertension |
| **Pegcetacoplan** | Hypertension<br>Hypokalemia<br>Headache<br>Gastrointestinal disturbances (nausea, diarrhea)<br>Injection-site reactions<br>Artificially prolonged activated partial thromboplastin time (interference with coagulation testing)<br>Increased serum C3 |
| **Iptacopan** | Headache<br>Hyperlipidemia<br>Hypertension<br>Metabolized by CYP2C8 |

## DISCLOSURES

Dr. Bassil has disclosed consulting for Mallinckrodt Inc. Dr. Cavanaugh has disclosed consulting for Cerium Pharmaceuticals, Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Travere Therapeutics, and Vera Therapeutics and acting as an advisor or review panel participant for Cerium Pharmaceuticals. Dr. Nakhoul has disclosed consulting for Akebia Therapeutics, Inc., Amgen, Boehringer Ingelheim, Calliditas Therapeutics, GSK, and Otsuka Pharmaceuticals. Dr. Taliercio has disclosed acting as an advisor or review panel participant for Amgen, Apellis Pharmaceuticals, and Calliditas Therapeutics. Dr. Mehdi has disclosed acting as an advisor or review panel participant for Alexion, Calliditas Therapeutics, and Novartis and teaching and speaking for Apellis Pharmaceuticals and GSK. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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***Address:*** *Ali Mehdi, MD, MEd, Department of Kidney Medicine, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; mehdia@CCF.org*

ADAM J. BROWN, MD, Associate Editor

**Adam J. Brown, MD**
Department of Rheumatologic and Immunologic Disease, Cleveland Clinic, Cleveland, OH; Clinical Instructor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Clinical application of the complement system: A historical perspective

THE COMPLEMENT CASCADE is something you memorize for Step 1 in your medical training, hoping to never have to think about it again. In this month's *Journal*, Salupo et al[1] present an overview of the complement cascade as well as current and future therapeutics targeting the cascade. In light of the developments outlined by Salupo et al,[1] it might be time to open that immunology book and give complement another look: over 40 proteins cascading through the blood, mostly in precursor forms (named in a combination of upper- and lowercase letters and numbers), requiring enzymatic activation to form larger complexes (with a new combination of letters and numbers) and cleave other components, leading to a variety of actions including opsonization of bacteria, chemoattraction of neutrophils, and direct cell lysis via the membrane attack complex.[2]

***Associate Editor, Adam Brown, MD, discusses an angle related to the article "Complement inhibition: A whole new world" on page 227.***

It's a lot, I know. To better *appreciate* the complement system, it's important to trace how our understanding of it evolved over more than a century, starting with its discovery in the late 19th century, then its application in the laboratory, which changed how we diagnose infection, and then the slow unraveling of its role in the pathophysiology of disease from both overactivity to deficiency.

## HOW WAS THIS CASCADE OF PROTEINS DISCOVERED?

Looking at this complex system of proteins, it's easy to wonder how someone could have possibly discovered it, especially in the late 1800s, at the dawn of our understanding of the immune system. I'll provide a little background: scientists were trying to understand how the immune system killed organisms via innate (Dr. Elie Metchnikoff describing phagocytosis) and humoral immunity. To better understand humoral immunity, Dr. Richard Pfeiffer injected cholera bacteria into the abdominal cavity of guinea pigs previously immunized to cholera, then collected serum from the animals and visualized the bacteria losing motility and eventually dying.[3] This protection against cholera was unique to the cholera organism—animals immune to cholera would die when inoculated with other bacterial organisms.

Interestingly, serum from immunized guinea pigs added to cultured cholera ex vivo did not kill the cholera bacteria.[3] Pfeiffer hypothesized that cells within the abdominal cavity of the guinea pigs, along with the immunized serum, were necessary to cause the bacteriolysis.

Around this time, Belgian scientist Dr. Jules Bordet was working at the Pasteur Institute, studying Pfeiffer's work. Bordet realized that immunized serum *can* kill cholera bacteria ex vivo, as long as the sample was fresh and hadn't been exposed to significant temperature fluctuation. The serum would lose its bacteriolytic ability if exposed to temperatures above 55°C (131°F). This was different from antibodies, which were known to be heat stable. Interestingly, if the serum was heated above 55°C and serum from a *nonimmunized* guinea pig was added to it, the original antiserum would *regain* its bacteriolytic properties. Bordet concluded that bacteriolysis was dependent on organism-*specific* antibodies and a heat-sensitive component *not specific* to the organism that complements the antibody killing

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of bacteria.[4] He described what would eventually be called *complement*.

It would take decades of work to unravel the full spectrum of the complexity of the cascade. Much to the consternation of medical students, the individual components of the cascade were named in the order of discovery, not their place within the enzymatic cascade.

## BRINGING COMPLEMENT TO DIAGNOSTICS: COMPLEMENT FIXATION TESTING

In 1901, Dr. Bordet developed a multistep laboratory test to check serum for antibodies to certain infections, taking advantage of the heat lability of complement and heat stability of antibodies. The complement fixation test was developed decades before the extent of the cascade was known. Here is an overview of how the test is conducted and its results interpreted[5]:

**First**, draw the patient's blood, centrifuge it to separate the cells from serum, then heat the serum to 56°C (132.8°F), denaturing any complement in the serum but still preserving antibodies.

**Then**, add a standardized amount of complement (usually from a guinea pig) along with the antigen of interest to the heated serum and incubate the combination for multiple hours at 4°C (39.2°F). If antibodies are present in the serum, the antibodies will bind to the antigen, forming an antibody-antigen complex, triggering complement activation (and complement consumption).

**Finally**, add antibody-coated sheep red blood cells to the serum.

- If antibodies were initially present against the antigen, then complement will have been consumed and will not be available to lyse the antibody-coated red blood cells and the red blood cells will remain whole; this is a positive test.
- If antibodies were *not* initially present, complement will still be present in the serum and will be activated by the antibody-coated sheep red blood cells and cause hemolysis; this is a negative test.

It's impressive that scientists elucidated this immunologic phenomenon for diagnostics in 1901, as it's hard to wrap your mind around it in 2026.

Complement fixation allowed for a giant leap in diagnosing certain infections. Dr. August von Wasserman used the complement fixation test in 1906 to diagnose syphilis. Up to this point, syphilis was diagnosed based on pattern recognition of signs and symptoms, and latent cases were often missed. An initial barrier to using complement fixation to test for syphilis was that *Treponema pallidum* couldn't be cultured, so it was difficult to obtain the bacteria to use as an antigen in the test. Wasserman got around this by harvesting tissue extracts from infected chimpanzees or the livers of human fetuses who died of syphilis. Once the Wasserman test was established, asymptomatic persons were tested in various settings, including prenatal clinics, military recruitment centers, and hospitals, revealing the true prevalence of syphilis as much higher than previously understood, over 10% in some populations.[6]

As syphilis testing became more widespread, multiple false positives were found in patients with other chronic infections, including tuberculosis and leprosy. A major surprise occurred in 1907 when it was found that healthy tissue from animals, particularly the myocardium of guinea pigs, could be used as the antigen in the Wasserman test. Over time it was discovered that chronic infections, including syphilis, cause tissue damage, releasing phospholipids from the tissue. The Wasserman reaction was detecting antibodies to the tissue damage, *not* antibodies to *T pallidum*, which also explained its positive rates in other chronic infections. Despite the lack of specificity, the Wasserman test was found to be a useful screening test for a disease that previously relied on symptoms and pattern recognition for diagnosis.

The clinical manifestations of syphilis are broad and heterogenous. In 1909, Wasserman testing was performed on a group of women who had multiple spontaneous abortions. It was thought at the time that the abortions were caused by syphilis, and this thinking was confirmed (falsely) when many of the woman tested positive. Utilizing animal myocardium allowed for the widespread testing of syphilis, but it wasn't until the 1940s that the antigen cardiolipin was described.[5] It would be decades later that anticardiolipin antibodies were linked to thrombosis and recurrent miscarriages.

Taking advantage of the complement system to diagnose a disease that previously relied on active signs and symptoms for diagnosis revolutionized our understanding of syphilis. The complement fixation test was developed without an understanding of the extent of the cascade or its function within the immune system. Over the next decades, the array of proteins within the complement cascade was elucidated, and testing for complement function, including testing for individual components, became possible, allowing for an understanding of complement's role in disease.

## COMPLEMENT'S ROLE IN DISEASE

It took many decades for the biological role of complement to be defined and its role in the pathophysiology

of disease explained. In 1951, Vaughan and colleagues[7] at Harvard published an article evaluating complement activity in 4 patients with active systemic lupus erythematosus (SLE), all of whom had low complement levels due to increased complement activity. The patients were treated with adrenocorticotropic hormone (glucocorticoid) therapy and experienced a clinical response along with normalization of complement levels.

In 1953, a report from the Mayo Clinic confirmed these findings by evaluating 27 patients with lupus compared with 60 controls. This study confirmed that patients with lupus had decreased measurable complement, and for the first time found a correlation between decreased complement and increased albuminuria, indicating kidney involvement.[8] Testing for C3 and C4 in patients with SLE is now a standard method to help determine disease activity. We now know that the classical cascade is triggered in a number of immune complex–mediated diseases such as SLE, cryoglobulinemic vasculitis, urticarial vasculitis, and serum sickness.

Not only is complement important in the pathophysiology of multiple autoimmune diseases, but also a *deficiency* of components of the cascade can increase risk of infection with certain organisms. In 1974 at the University of Rochester, an 18-year-old woman presented with fevers and joint pain. She was eventually diagnosed with disseminated gonococcal infection, but because SLE was on the differential, complement levels were checked and were found to be low. Initially, the low complement activity was thought to be secondary to immune complex formation and complement activation due to the infection, but additional testing demonstrated a deficiency of C6, which is the first component of the membrane attack complex critical for bacteriolysis.[9]

Two years later, a 6-year-old was hospitalized with *Neisseria* meningitis for the third time. The young boy was also found to be deficient in C6, accounting for his repeated cases of the disease.[10] These cases led to our understanding of the importance of the terminal complement components, mainly those leading to formation of the membrane attack complex, in fighting encapsulated organisms like *Neisseria meningitidis* and *Neisseria gonorrhoeae*.

## OUR CURRENT UNDERSTANDING OF COMPLEMENT

The complement cascade is an intricate assortment of proteins cleaving and combining with one another to form difficult-to-memorize complexes. Well before the full extent of the cascade was appreciated, researchers took advantage of complement function in the laboratory to test for previously difficult-to-diagnose diseases such as syphilis. As laboratory techniques improved, we were able to measure complement activity, eventually measuring individual components of the cascade, allowing activity of complement to be recognized in certain diseases like SLE. Low levels of terminal complement were found to be associated with recurrent infections with encapsulated bacterial organisms. Measuring complement gave us a better appreciation of its role in disease, both in overactivity and deficiency. Now, our understanding of complement has evolved to therapeutic targeting of components of the cascade in a wide range of diseases, making it necessary for us to dust off the immunology book sitting on the shelf and figure out just what we're shooting at.

## DISCLOSURES

Dr. Brown reported consulting for Amgen and Sanofi and teaching and speaking for Amgen, Chemocentryx, and Sanofi.

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***Address:*** *Adam J. Brown, MD, Department of Rheumatologic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; browna22@ccf.org*

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**Vignan Manne, MD**
Department of Internal Medicine, Kirk Kerkorian School of Medicine at University of Nevada, Las Vegas, Las Vegas, NV

**Amber Champion, MD**
Department of Internal Medicine, Kirk Kerkorian School of Medicine at University of Nevada, Las Vegas, Las Vegas, NV

# Gastrointestinal disorders in patients with diabetes mellitus: A practical guide for primary care

## ABSTRACT

Gastrointestinal disorders are common in patients with diabetes mellitus and can be linked to diabetes itself, its complications, or medications used to treat it. These disorders include gastroesophageal reflux, gastroparesis, enteropathy manifesting clinically with constipation or diarrhea, and metabolic dysfunction–associated steatotic liver disease. Timely diagnosis and management of these disorders can improve patients' quality of life. The authors provide clinically practical advice on when and how to screen for common diabetes-related gastrointestinal disorders and review the management of these disorders in the primary care setting.

## KEY POINTS

- Diabetes mellitus affects an increasingly large number of patients and can cause a wide range of gastrointestinal pathologies.
- The most prevalent gastrointestinal disorders linked to diabetes are gastroparesis and metabolic dysfunction–associated steatotic liver disease, with both having a prevalence up to 70%.
- The pathophysiology of diabetes mellitus–associated gastrointestinal complications is generally related to poor glycemic control and can be prevented with intense glycemic control.

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Approximately 500 million people worldwide are living with diabetes, and this number is expected to grow to 700 million by 2045.[1] Diabetes mellitus is linked to a wide range of gastrointestinal pathology. Gastrointestinal disorders associated with diabetes mellitus include gastroesophageal reflux disease, gastroparesis, small intestinal bacterial overgrowth, metabolic dysfunction–associated steatotic liver disease (MASLD), and acute pancreatitis.[1] Diabetic neuropathy plays a large role in the pathogenesis of these disorders, from initial blunting of symptoms to eventual dysmotility that can occur across the entire gastrointestinal tract.

Patients with diabetes and coexisting gastrointestinal issues generally first seek care in the primary care setting due to symptoms such as reflux, nausea, vomiting, bloating, diarrhea, and constipation. Awareness of the protean effects of diabetes and diabetes medications on the gastrointestinal system is important, as appropriate and timely diagnosis of gastrointestinal disorders can improve quality of life for these patients.

This review addresses the epidemiology and pathophysiology of diabetes-related disorders affecting the esophagus, stomach, small and large intestine, liver, and pancreas. Included is discussion of medications that could be implicated, practical advice on when and how to screen, management and referral recommendations, and data to support recommended interventions.

**TABLE 1**
**GerdQ: Gastroesophageal reflux disease self-assessment**

| Questions about symptoms in previous week | Number of days symptoms were present | | | |
|---|---|---|---|---|
| | 0 | 1 | 2–3 | 4–7 |
| How often did you have a burning feeling behind your breastbone (heartburn)? | 0 | 1 | 2 | 3 |
| How often did you have stomach contents moving upwards to your throat or mouth (regurgitation)? | 0 | 1 | 2 | 3 |
| How often did you have pain in the center of the upper stomach? | 0 | 1 | 2 | 3 |
| How often did you have nausea? | 0 | 1 | 2 | 3 |
| How often did you have difficulty getting a good night's sleep because of heartburn, regurgitation, or both? | 0 | 1 | 2 | 3 |
| How often did you take additional medication for your heartburn, regurgitation, or both other than what the physician told you to take (such as Maalox)? | 0 | 1 | 2 | 3 |
| **Scoring**<br>≥ 8 indicates high likelihood patient has GERD[a]<br>< 8 indicates low likelihood patient has GERD | | | | |

[a]Patients with a score ≥ 8 who do not have any alarm symptoms (weight loss, dysphagia, bleeding, vomiting, anemia) should be started on a proton pump inhibitor.

Adapted from Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2009; 30(10):1030–1038. doi:10.1111/j.1365-2036.2009.04142.x with permission of John Wiley and Sons.

## GASTROESOPHAGEAL REFLUX

Individuals with diabetes mellitus are more predisposed to developing retrograde movement of acid from the stomach into the esophagus compared with those without diabetes.[2] Proposed mechanisms for abnormal gastroesophageal reflux include delayed gastric emptying and impaired esophageal motility due to neuropathy caused by diabetes.[3] In addition, it is hypothesized that autonomic neuropathy due to acute or chronic hyperglycemia can increase the frequency of transient relaxation of the lower esophageal sphincter, ie, relaxation without a swallow, which can lead to gastroesophageal reflux disease.[2]

The exact prevalence of gastroesophageal reflux disease in patients with diabetes mellitus is unclear; however, one study reported that 25% of patients with type 2 diabetes mellitus had heartburn and chest discomfort after eating, consistent with gastroesophageal reflux disease.[4] In this study, reflux symptoms occurred more often in those with poorer glycemic control, as reflected by the presence of diabetes complications including retinopathy, nephropathy, or neuropathy.

### Screening and management

Gastroesophageal reflux disease should be considered when patients present with typical symptoms such as substernal burning ("heartburn"), pain in the middle of the stomach, or regurgitation along with the need for over-the-counter antacids to resolve these symptoms. The GerdQ questionnaire, a 6-item diagnostic tool developed using data from primary care patients with upper gastrointestinal symptoms, can be used before making a gastroenterology referral (**Table 1**).[5] Patients with a score of 8 or higher (indicating a high likelihood of gastroesophageal reflux disease) who do not have any alarm features (weight loss, dysphagia, bleeding [hematemesis, melena], vomiting, anemia) should undergo an 8-week trial of empiric treatment with a proton pump inhibitor, as recommended by the current American College of Gastroenterology guideline.[6]

Gastroenterology referral is indicated for patients who have alarm symptoms, patients whose symptoms do not respond to proton pump inhibitor therapy, or patients whose symptoms return after proton pump inhibitors are discontinued (**Figure 1**).

The response of symptoms to proton pump inhibitor therapy depends on the degree of glycemic control. Fur-

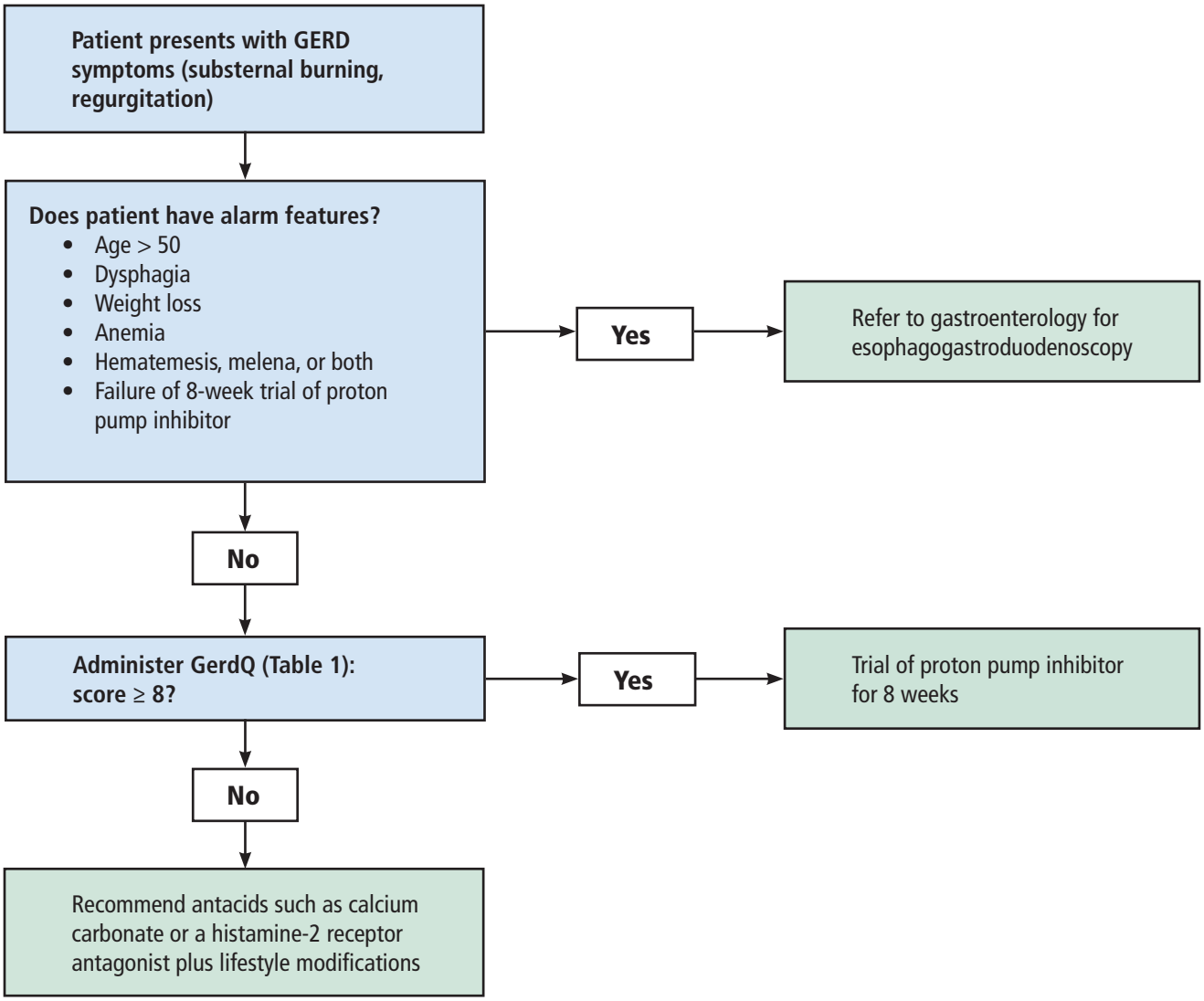


**Figure 1.** Algorithm for assessment of gastroesophageal reflux disease (GERD) symptoms.

ther, a case-control study found that obesity concurrent with diabetes mellitus was associated with failure of proton pump inhibitor therapy.[7] Improving glycemic control can alleviate symptoms, increase responsiveness to therapy, and reduce the need for future nonessential endoscopic screening.

### Increased risk for esophageal carcinoma

Long-standing gastroesophageal reflux disease can lead to development of Barrett esophagus and predispose patients to esophageal adenocarcinoma. In a case-control study of male veterans undergoing routine colorectal cancer screening, 821 participants were recruited for additional upper endoscopy. Among these, 70 (8.5%) were diagnosed with Barrett esophagus, of whom 15 (21%) had preexisting diabetes.[8] In a meta-analysis of observational studies, diabetes mellitus was associated with an increased risk of esophageal carcinoma (relative risk 2.72, 95% confidence interval 1.01–4.46).[9] In a Veterans Affairs database study, 30.8% of patients with esophageal carcinoma had concomitant diabetes mellitus, and logistic regression showed an association between diabetes and risk of esophageal cancer (odds ratio 2.23, 95% confidence interval 1.75–2.82).[10]

Although diabetes mellitus is a modest risk factor for esophageal carcinoma, current evidence does not support screening for esophageal carcinoma. In patients with diabetes mellitus and known gastroesophageal

**TABLE 2**
**Medications that can cause gastrointestinal complications in patients with diabetes**

| Gastrointestinal complication | Medication |
|---|---|
| Gastroparesis and delayed gastric emptying | Glucagon-like peptide 1 receptor agonists<br>Aluminum hydroxide antacids<br>Anticholinergics<br>Diphenhydramine<br>Beta-adrenergic agonists<br>Calcium channel blockers<br>Cyclosporine<br>Histamine-2 receptor blockers<br>Levodopa<br>Lithium<br>Tricyclic antidepressants<br>Proton pump inhibitors<br>Phenothiazines<br>Opioids<br>Ondansetron |
| Diarrhea | Metformin<br>Artificial sweeteners |
| Constipation | Semaglutide |
| Cholelithiasis | Glucagon-like peptide 1 receptor agonists |
| Cholecystitis | Dipeptidyl peptidase 4 inhibitors<br>Glucagon-like peptide 1 receptor agonists |

reflux disease, we recommend counseling on lifestyle modifications with weight loss and smoking cessation to ameliorate preventable risk factors associated with esophageal adenocarcinoma.

## GASTROPARESIS

Gastroparesis is defined as delayed gastric emptying without mechanical obstruction. The pathogenesis of gastroparesis in patients with diabetes remains poorly understood, but it is accepted that hyperglycemia plays a role. Hyperglycemia reduces the number of "pacemaker" interstitial cells of Cajal in gastrointestinal smooth muscle, leading to improper synchronization of smooth muscle in the stomach.[11]

The overall prevalence of gastroparesis in patients with diabetes is 9.3%.[12] In a population-based cohort study, the 10-year cumulative incidence of gastroparesis was 5.2% in patients with type 1 diabetes and 1.0% in those with type 2 diabetes.[13] Bytzer et al [14] found coexisting peripheral neuropathy to be significantly associated with the development of gastroparesis. Analysis of data from the Diabetes Control and Complications Trial–Epidemiology of Diabetes Interventions and Complications study showed that gastroparesis occurs in patients who have had type 1 diabetes mellitus for at least 10 years.[15]

### Screening and management

Primary care clinicians can screen for gastroparesis in patients with diabetes mellitus by asking about symptoms of nausea, satiety, and bloating. If these symptoms are present, a thorough medication reconciliation can be helpful. Many medications are known to reduce gastrointestinal motility (**Table 2**), including glucagon-like peptide (GLP) 1 receptor agonists used to treat type 2 diabetes (more on these medications below). Patients whose symptoms persist for at least 1 month after medication reconciliation should be referred to gastroenterology for esophagogastroduodenoscopy to rule out mechanical obstruction.

Primary care clinicians can educate patients on how to intensify glycemic control and modify their diet around small-particle, low-fat food, both of which can decrease the risk of gastroparesis.[16] However, achieving glycemic control in patients who have developed gastroparesis is challenging. Symptoms interfere with regular meals, and patients may withhold insulin to avoid hypoglycemia.

To address this challenge, investigators have explored the use of continuous subcutaneous insulin infusion therapy in patients with diabetic gastroparesis. In a small UK trial of patients with type 1 diabetes, continuous subcutaneous insulin infusions were shown to be effective in reducing blood glucose variability as well as reducing hospitalizations for gastroparesis.[17] In an open-label pilot study, continuous subcutaneous insulin infusions along with continuous glucose monitoring safely reduced patients' time in hypoglycemia and improved hemoglobin A1c and gastroparesis symptoms.[18]

### GLP-1 receptor agonists and gastric motility

It is well known that GLP-1 receptor agonists can cause delayed gastric emptying and gastroparesis, and that they are associated with other gastrointestinal complications such as nausea and vomiting, constipation, cholelithiasis, and cholecystitis. These complications are related to the effect of GLP-1 receptor agonists on gastrointestinal motility. In the primary care setting, starting a GLP-1 receptor agonist at a high dose or escalating a dose too quickly can lead to complications. It is recommended that clinicians start patients at the lowest dose and discontinue treatment if symptoms of gastroparesis occur.[19]

## SMALL INTESTINAL BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth is an alteration in the quantity and type of bacteria in the small intestine. Recent data indicate that a normal gut microbiome consists primarily of *Firmicutes*, *Bacteroides*, and *Actinobacteria*, which respectively make up 60% to 80%, 20% to 30%, and 10% of the gut microbiota.[20] However, in several clinical trials the ratio of *Firmicutes* to *Bacteroides* was found to be much lower in patients with diabetes mellitus.[21]

Diabetes mellitus causes decreased motility of the small intestine, enabling bacterial stasis, dysbiosis, and subsequent overgrowth. These changes can increase bacterial byproducts such as ammonia, fatty acids, and toxins that can damage the gut lining, ultimately decreasing normal absorption of carbohydrates and fat.[22] The clinical effects are abdominal bloating, discomfort, and diarrhea.

In a small prospective study, small intestinal bacterial overgrowth was diagnosed in 43% (15 or 35) of patients with type 1 or type 2 diabetes mellitus who had chronic diarrhea.[23] The prevalence of small intestinal bacterial overgrowth does not differ significantly in patients with type 2 diabetes vs type 1 diabetes mellitus.[24]

### Screening and management

Primary care clinicians should refer patients to gastroenterology to screen for small intestinal bacterial overgrowth when they have unexplained chronic diarrhea, bloating, or signs and symptoms of persistent, significant unintentional weight loss and malnutrition.[22]

Addressing any underlying disease or condition is a key component of treating small intestinal bacterial overgrowth. In patients with long-standing type 1 diabetes mellitus, proper glycemic control can improve gastrointestinal symptoms caused by small intestinal bacterial overgrowth.[25] We can hypothesize that better glycemic control also can improve symptoms in patients with type 2 diabetes.

Primary care clinicians can also suggest that patients try a low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet to relieve symptoms, but data remain inconclusive for this modality.[26]

## LARGE INTESTINE: DIARRHEA AND CONSTIPATION

Cohort studies have found that chronic constipation affects between 15% and 25% of patients with diabetes mellitus, and constipation seems to be significantly more common in patients with autonomic neuropathy than in those without neuropathy.[27] Diabetic neuropathy can lead to impaired rectal sensation, and can also affect the function of the anal sphincters and the rectum, hindering the passage of stool.[27] Further, about 20% of patients with diabetes complain of diarrhea and fecal incontinence.[28]

### Management

Notably, there are no published data on diagnostic testing in patients with diabetes who present with clinical symptoms of diarrhea or constipation, nor are there algorithms for screening these patients.

Artificial sweeteners that patients may use as alternatives to sugar are commonly associated with diarrhea, so clinicians should ask patients if these are a regular part of their diet.

GLP-1 receptor agonists and metformin are notably associated with gastrointestinal adverse effects, including diarrhea, nausea, indigestion, vomiting, and constipation. Patients' medications should be reviewed. If a patient's gastrointestinal symptoms are attributable to medications, clinicians can switch to agents from a different drug class, but switching to an alternative formulation also may be effective. For example, a large meta-analysis found that the extended-release formulation of metformin was associated with reduced bloating, vomiting, and abdominal pain compared with the immediate-release formulation.[29] In a prospective cohort study in Italy of patients who were intolerant to immediate-release metformin, 88% of patients reported improvement in diarrhea after taking extended-release metformin.[30]

## METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

MASLD is characterized by fat accumulation in the liver that is not linked to alcohol consumption or other toxins. MASLD is common in patients with type 2 diabetes; its prevalence can be as high as 69.5% in this population.[31]

Type 2 diabetes contributes to MASLD by promoting accumulation of fat in the liver. Hyperglycemia and insulin resistance cause the liver to synthesize more glucose, providing substrates for hepatic lipogenesis, which exceeds lipolysis.[32] The result is an increase in hepatic free fatty acids, which are toxic to hepatocytes. This process correlates with higher levels of insulin and insulin resistance, which drives the synthesis of free fatty acids.

### Screening and management

Primary care clinicians should screen patients for hepatic fibrosis, the most important determinant of

liver and nonliver outcomes in patients with MASLD. The American Diabetes Association[33] and American Association of Clinical Endocrinology,[34] along with other professional societies, recommend screening for MASLD and metabolic dysfunction–associated steatohepatitis in patients with obesity and prediabetes or with type 2 diabetes mellitus, as the pretest probability of hepatic steatosis in these populations is 70% or higher. For high-risk patients older than 35, clinicians can start by calculating a fibrosis-4 score; this measure uses age, levels of aspartate and alanine transaminases, and platelet count to estimate the amount of liver scarring[33]:

- Score less than 1.3: fibrosis can be reliably excluded
- Score between 1.3 and 2.67: liver ultrasonography with transient elastography to determine liver stiffness is recommended
- Score greater than 2.67: patient is at increased risk of advanced liver fibrosis and requires gastroenterology referral for further evaluation.[35]

**Weight loss.** Management of MASLD can be started in the primary care setting with a combination of lifestyle modification and weight management. Weight loss of at least 3% to 5% of total body weight can improve steatosis. Typically, more than 5% weight loss is needed to reverse steatohepatitis, and many studies suggest that more than 10% is needed to improve fibrosis, but responses can vary.[36]

**Exercise** has been shown to decrease insulin resistance, plasma aminotransferases, and steatosis. Aerobic activity and high-intensity activity potentially offer greater hepatic benefits than other types of exercise.[37] Current guidelines recommend moderate-intensity exercise for at least 150 minutes per week or 75 minutes of vigorous-intensity activity per week with resistance training 2 to 3 times per week.[38] Minimizing sedentary time with activities such as walking is also encouraged.

**Dietary approaches.** A diet incorporating high-fiber foods and unsaturated fats is generally recommended. Foods high in saturated fat and sugars such as sucrose or high-fructose corn syrup are associated with postprandial hypertriglyceridemia, insulin resistance, and ultimately a higher risk for MASLD or metabolic dysfunction–associated steatohepatitis; these foods should be limited.[39] It is best to avoid ultraprocessed foods and to reduce intake of saturated fats, simple sugars, and fructose.

No single nutritional approach has been found superior. Readily available nutritional approaches seem comparable in their ability to improve steatosis; these include low-fat and low-carbohydrate foods, Mediterranean dietary approaches to stop hypertension (the DASH [Dietary Approaches to Stop Hypertension] diet), high-protein foods, and intermittent fasting.

**A pharmacologic approach** to comorbid conditions such as type 2 diabetes mellitus with GLP-1 receptor agonists (ie, tirzepatide, semaglutide) can effectively reduce hemoglobin A1C levels, increase weight loss, and reduce liver fibrosis. Resmetirom and semaglutide are also approved by the US Food and Drug Administration for treatment of metabolic dysfunction–associated steatohepatitis and MASLD.[40]

## GALLSTONE DISEASE AND ACUTE PANCREATITIS

Gallstone disease is the most common cause of acute pancreatitis, accounting for 20% to 70% of pancreatitis cases worldwide.[41] Patients with diabetes have an increased incidence and prevalence of gallbladder disease,[42] which increases their risk for developing gallstone-related acute pancreatitis. The pathophysiology of acute pancreatitis in patients with diabetes is poorly understood, but studies have shown that patients with type 2 diabetes mellitus have a 3-fold greater risk of pancreatitis compared with patients without type 2 diabetes mellitus.[43]

Recent trials have shown no increased risk of pancreatitis with GLP-1 receptor agonists compared with placebo.[44] A systematic review and meta-analysis of long-term placebo-controlled, randomized controlled trials also demonstrated that treatment with a GLP-1 receptor agonist does not increase the risk of pancreatitis.[45]

Some patients may develop diabetes following an episode of acute pancreatitis, which is called type 3c diabetes mellitus, or pancreatogenic diabetes. The underlying pathophysiology is poorly understood. Recent systematic reviews and meta-analyses have shown that around 15% of patients develop diabetes within 1 year of an acute pancreatitis episode and the severity of the acute pancreatitis episode may impact the likelihood of developing diabetes in the future.[46] There are no current guidelines on screening for diabetes after an episode of acute pancreatitis.

## DISCLOSURES

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***Address:*** *Magnus Chun, MD, Department of Internal Medicine, Kirk Kerkorian School of Medicine at University of Nevada, Las Vegas, 625 Shadow Lane, Las Vegas, NV 89106; magnus.chun@unlv.edu*

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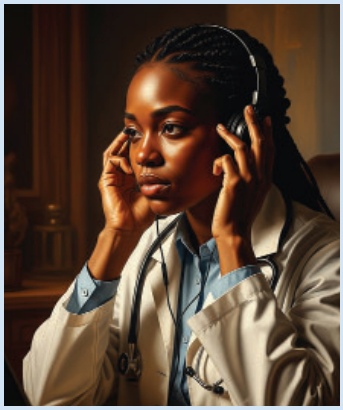

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